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DOT/FAA/AM-92/19

Tolerance of Beta Blocked Hypertensives During Orthostatic and Altitude Stresses

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April 1992

Final Report

U.S. Department
of Transportation
**Federal Aviation
Administration**

NOTICE

Technical Report Documentation Page

1. Report No.	2. Government Accession No.	3. Recipient's Catalog No.
DOT/FAA/AM-92/19		

4. Title and Subtitle	5. Report Date
TOLERANCE OF BETA BLOCKED HYPERTENSIVES DURING ORTHOSTATIC AND ALTITUDE STRESSES	September 1991
	6. Performing Organization Code
	8. Performing Organization Report No.

7. Author(s)	
Steven M. Teague, M.D. and Jerry R. Hordinsky, M.D.	

9. Performing Organization Name and Address	10. Work Unit No. (TRAIS)
FAA Civil Aeromedical Institute P. O. Box 25082 Oklahoma City, OK 73125	11. Contract or Grant No. DTFA-02-86-85098
	13. Type of Report and Period Covered
12. Sponsoring Agency Name and Address Office of Aviation Medicine Federal Aviation Administration 800 Independence Avenue, S.W. Washington, D.C. 20591	14. Sponsoring Agency Code

15. Supplementary Notes

16. Abstract

To evaluate the effects of orthostatic, altitude, and pharmacologic stresses upon civil aviation-specific performance, a double-blind, randomized, crossover trial of atenolol, 100mg, was designed and executed. Hypertensive males and females qualifying for the FAA class 3 certificate with mean age of 34 were studied during simulated altitude exposure to 12,500 ft, orthostatic stress, and moderate exercise. Seated lower body negative pressure to -40 mmHg supplied orthostatic stress simulating +2G vertical acceleration. A total of 160 lower body negative pressure tests were performed, 80 at ground and 80 at altitude. Beta-blockade caused a modest impairment in orthostatic tolerance. Five of the 80 lower body negative pressure runs at ground level were marked by intolerance, and all of those responses were in beta-blocked subjects. Of the 80 altitude runs, 30 were terminated for intolerance, of which 18 included beta-blockade. These findings had a Chi-square significance value of $P < .05$. The effect of altitude was significant at $P < .01$. In a modest exercise protocol (100 watts for 3 minutes) meant to be no more stressful than the exertional requirements of piloting an aircraft during adverse conditions, neither beta-blockade or altitude appeared to limit performance.Quantitative performance on a computerized cognitive battery clearly demonstrated impaired performance during lower body negative pressure stress at altitude. The degree of impairment was significant compared to a learning curve response at the $P < .001$ level. The degree of impairment was similar for placebo treated and beta-blocked subjects.

Monitoring of mean arterial pressure, heart rate, and stroke volume was necessary for quantitative analysis of hemodynamic responses to these stressors. These parameters demonstrated progressive decrements in systemic vascular resistance in intolerant subjects, implicating a defective peripheral autonomic nervous system response. Moreover, monitoring of systemic vascular resistance, blood pressure, and transcranial Doppler middle cerebral artery flow velocities allowed prediction of impending cognitive and hemodynamic collapse.

These data implicate the synergistic deleterious effects of beta-blockade and altitude in the potentiation of intolerance to orthostatic stress. These findings may have most revelance to the personnel of unpressurized aircraft who are being treated with beta-blocking drugs for hypertension. No common clinical parameter predicts subsequent intolerance. It appears that only formal stress testing will uncover orthostatic-prone individuals.

17. Key Words	18. Distribution Statement
Hypertension, Beta-blockers, Orthostatic Tolerance, Hypoxia, Medical Certification	Document is available to the public through the National Technical Information Service, Springfield, Virginia 22161

19. Security Classif. (of this report)	20. Security Classif. (of this page)	21. No. of Pages	22. Price
Unclassified	Unclassified	36	

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EXECUTIVE SUMMARY

Background

A study was initiated by the University of Oklahoma in October of 1986 that addressed a long-range Federal Aviation Administration (FAA) need to develop a standardized aviation-stress-specific human testing protocol, which could be used to assist in assessing the safety of specific medications employed by civilian pilots. Decisions to permit use of medications are currently based largely on non-aviation related clinical data; and, although very thoroughly executed, such decisions would be improved by the availability of relevant performance data. Additionally, the National Transportation Safety Board's Class III, Longer Term Action, #A-84-96, recommended attention to research addressing potential effects of both licit and illicit drugs on human performance in all transportation modes.

The study herein described was defined to address a subset of overall FAA research needs and NTSB research recommendations. Specifically, the University of Oklahoma, represented by the principal investigator, Dr. Steve Teague, developed a testing protocol adaptable primarily to cardiovascular-acting drugs; and, to the antihypertensive atenolol (a beta-blocking agent that is the most prevalent of those beta-blocking agents certified by the FAA for use in civilian pilots).

Methods

The protocol, which is described in detail in the attached primary report, exposed the test subjects to stressors considered representative of "maximum" civil aviation stressors, defined for the purposes of this study as (a) 12,500 feet altitude exposure in a hypobaric chamber, (b) = 2.0 Gz accelerative stress simulated in a seated lower body negative pressure (LBNP) device, (c) 75-100 watts exercise output on a bicycle ergometer, and (d) part-task simulation of required flying skills using a computer screen presentation and keyboard. These levels of stress are normally exceeded only in emergencies or in unique subsets of civilian aviation duties. For example, altitude exposures above 12,500 feet are normally compensated with supplemental oxygen, and higher Gz levels are developed normally only in aerobatic or in high maneuvering applications, such as agricultural spraying.

This protocol that was followed can be characterized as a double-blind randomized placebo controlled investigation of responses to atenolol. All subjects (15 males and 5 females) qualified for the study via physical examinations based on FAA Class III certification standards, and also had entry blood pressures of 140/90 mm Hg or greater.

During the approximately 8 months of hypobaric chamber-based testing, which was carried out by the University of Oklahoma staff in a collaborative effort with FAA Civil Aeromedical Research and Education Divisions at CAMI, each subject was exposed to the multi-stressor sequence at approximately 1 and 3 months of both the placebo and drug phases of the study. Appropriate crossover time was factored into the study design. The noninvasive methodologies employed in the study included continuous electrocardiography, an automated differential transducer sphygmomanometer, a transthoracic bio-impedance monitoring device (to evaluate cardiac pump function), continuous wave Doppler monitoring (to further assess cardiac function), and a transcranial Doppler (to evaluate cerebral blood flow velocities).

Results

Each subject had 4 test days, with 1 at ground level and 1 altitude test session per test day; thus the entire collective of test sessions numbered 160 (20 subjects X 4 test days X 2 test sessions per day). The monitoring methodology permitted successful delineation of physiological and performance decrement in this test collective. All subjects completed the extended testing sequence.

Of the 160 test sessions, 35 were terminated for hemodynamic intolerance. Only 5 intolerant responses were recorded at ground, and theses were attributed to beta-blockade. The remaining 30 intolerant responses were seen at altitude, and 60% of these were attributed to the combined effects of altitude and beta-blockade. Intolerance to hemodynamic stress (lower body negative pressure) at altitude appears to be accompanied by progressive vasodilation in which the heart remains relatively unimpaired and progressive augmentation of stroke volume is observed. This cannot be described a cardiovascular presyncope, but rather a phenomenon of arteriolar resistance.

The computer-based cognitive testing in this aviation-specific stress environment permits quantitative assessment of individual and cumulative effects of the stressors; however, this cognitive impairment was principally the end result of significant central hemodynamic compromise, rather than premonitory decrement in cognitive function prior to onset of cardiovascular symptomatology.

Conclusions

Thus, for the medication studied, we would predict substantive physiological and performance decrement if a pilot on such medication is exposed to orthostatic stressors equivalent to or higher than the +2 Gz equivalent herein studied, and, especially, orthostatic stressors combined with altitude exposure.

Extrapolating to other dosages of atenolol and to other beta-blockers can only be effected cautiously. However,a systematic methodology has been developed and introduced that can demonstrate the pattern of physiological and performance decrement induced by any class of antihypertensive medication and perhaps even by many other classes of cardiovascular and central nervous system active medications. New entrants into the pharmacological armamentarium can be evaluated for specific civil aviation medicine relevance using this protocol.

The final contract report of this research submitted by Dr. Steve Teague is presented. Dr. Teague completed this work while at the University of Oklahoma; he currently is affiliated with Case Western Reserve University in Cleveland, Ohio.

LEGEND ABBREVIATIONS IN FIGURES AND TABLES

ALT	altitude
AVG	average
BAT	battery
BPD	diastolic blood pressure
BPM	mean blood pressure
BPS	systolic blood pressure
DV	diastolic velocity
GND	ground
HCT	hematocrit
HR	heart rate
INTOL	intolerant
LBNP	lower body negative pressure
MAP	mean arterial pressure
MV	mean velocity
N	group number
PT	patient
PV	peak velocity
S/D	systolic-to-diastolic ratio
STD, SD, STD DEV	standard deviation
SV	stroke volume
SVR	systemic vascular resistance
T	time
TFI	bioimpedance thoracic fluid index
TOL	tolerant

TOLERANCE OF BETA BLOCKED HYPERTENSIVES DURING ORTHOSTATIC AND ALTITUDE STRESSES

INTRODUCTION

Sudden incapacitation poses the greatest medical risks to commercial and private air travel.[1-4] The chief medical concerns causing sudden incapacitation include acute myocardial infarction, cerebral vascular thrombosis, and seizure. In the adult population, common etiologic factors responsible for these acute medical syndromes include uncontrolled hypertension and advanced atherosclerosis. The previous 2 decades have shown remarkable reductions in the incidence of myocardial infarction and stroke in the general population.[5-8] The reasons for these reductions include a heightened public awareness of the cardiovascular complications of tobacco use, uncontrolled hypertension, and uncontrolled hypercholesterolemia.

Effective antihypertensive agents have made the control of hypertension possible in every hypertensive. In addition, newer anticholesterol agents have made cholesterol control possible for many patients untreatable with previous drugs or diet alone. Thus, it is probable that continued reductions in myocardial infarction and stroke will be experienced in the ensuing decades. It is plausible that civilian aviation medical research should now turn from the study of myocardial infarction and stroke in the aviation environment to the evaluation of potentially deleterious hemodynamic consequences of the drugs that control hypertension and atherosclerosis.

The antihypertensives, particularly, deserve special attention in that they block the central vasomotor centers, inhibit peripheral vasoconstriction, or deplete the vascular space of sodium and water. In many hypertensive patients, these therapies result in mild orthostatic intolerance, as manifested by dizziness upon standing.[10,11] Civilian aviators are also routinely exposed to orthostatic stresses.[12-16] In addition, evasive maneuvers or emergency situations could expose crew and passengers to accelerations of greater degree and duration. The FAA has licensed over 15,000 aviators to fly with the diagnosis of hypertension.[17,18] It remains to be established whether the orthostatic tolerance of treated hypertensive airmen would be sufficient to maintain functional status during routine or unusual orthostatic stress.

Moreover, the aviation environment often imposes the effects of altitude, namely hypobaria and hypoxia. These physical stresses could heighten orthostatic intolerance, and potentiate deleterious effects of agents that are used to alter vascular responses.[19-20]

These issues led us to pose the following key questions:

1. Does beta-blockade compromise orthostatic tolerance?
2. Does altitude compromise orthostatic tolerance?
3. Do the combined effects of beta-blockade and altitude impair exercise performance?
4. Do the combined effects of beta-blockade and altitude compromise cognitive performance?
5. Can a stress protocol be designed to answer questions 1-4?
6. Can a noninvasive physiologic monitoring system be developed to assess hemodynamic and cognitive responses to the stresses in questions 1-4?
7. What physiologic factors predict orthostatic intolerance?

STUDY DESIGN

Subjects

We recruited fifteen males and five females from the general population with a mean age of 34 (range 18 to 52). Individuals were qualified for the study by meeting physical standards as specified for the FAA class 3 certificate, achieving age predicted target heart rate during treadmill exercise, and an entry blood pressure of 140/90 or greater. All subjects had been advised by their personal physicians of hypertension, and 12 subjects were under active treatment with antihypertensive agents. No subject had a history of fainting, syncope, or orthostatic intolerance.

Protocol

The protocol design was a placebo controlled double-blind, crossover study of atenolol, 100mg, daily (Figure 1). This study lasted 6 months. At time 0, the subjects discontinued all medications and half were randomized to atenolol, and half to placebo. At the end of 1 month, both groups underwent the first test battery (Table 1). At the end of month 3, subjects underwent the second test battery. At that time, each half group crossed over to the opposite medication, and were tested in 1 month at test battery number 3. At month 6, the fourth and final test battery was applied. The subjects were then removed from test drugs, the drug code was broken, and the subjects were counseled regarding findings during the

study. Subjects exited the study on prestudy medications. All 20 subjects entering the protocol exited the protocol, and no subject failed to complete any test battery.

researchers, the research subject proceeded through the battery, which lasted approximately 20 minutes. The test could be scored as total throughput, or correct hits per minute for the 20-minute period. An additional parameter, average throughput, was also calculated, defined as

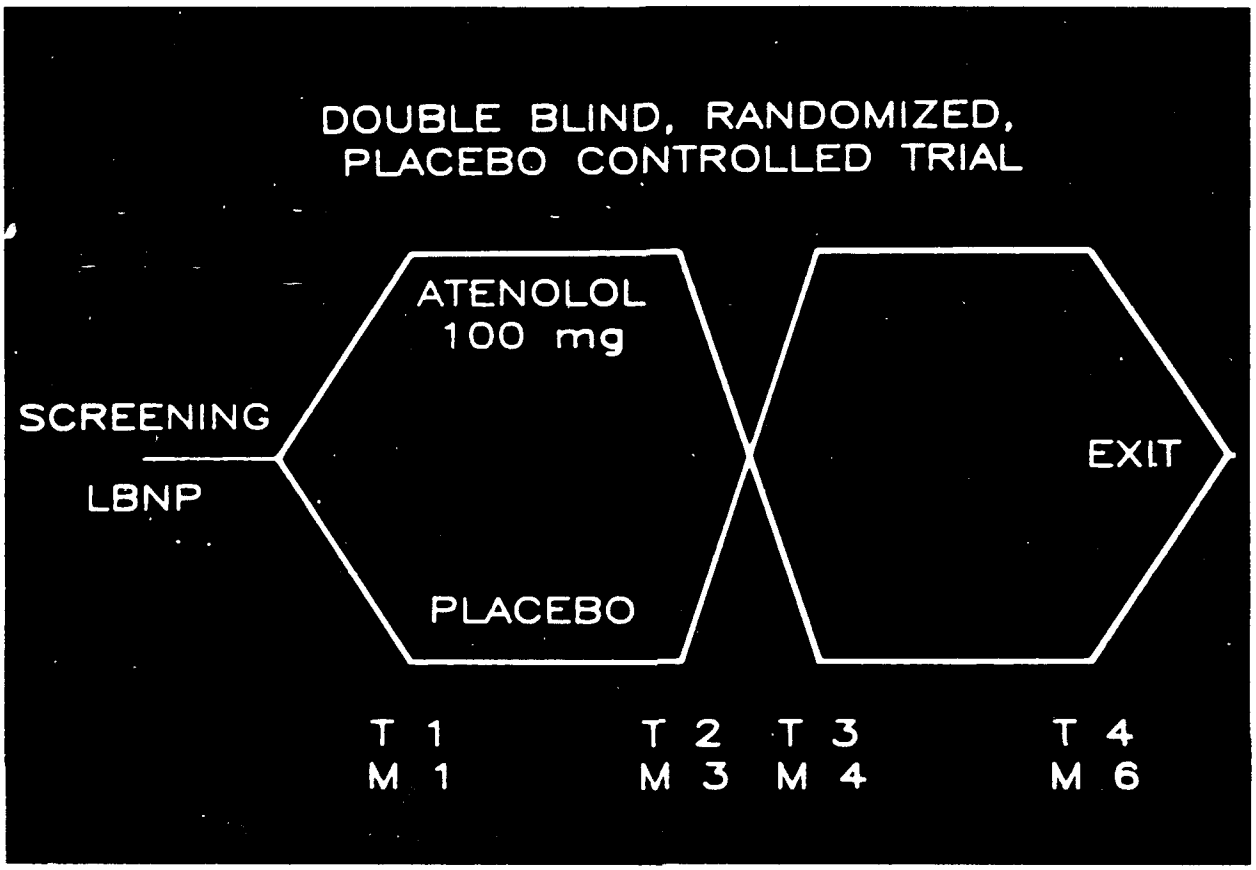

Figure 1. Schematic representation of the double-blind, randomized placebo crossover trial of atenolol used in this study. T=test; M=Month; LBNP=lower body negative pressure.

Test Battery

The test battery consisted of 5 components (Table I). The first component included a brief interval history and physical examination on the morning of the testing. Blood pressure and pulse was recorded supine and standing, and a blood specimen was drawn for hematocrit, sodium, and creatinine.

The second component consisted of cognitive performance evaluation. We modified the cognitive performance battery developed by Dr. David Thorn at Walter Reed Medical Center for this purpose.[21,22] The test battery is a computer-based modular assessment of spatial reasoning, logical reasoning, short-term memory, and reaction time. Each module can be scored in a quantitative fashion. Following instruction by one of the

TEST BATTERY
1. Prestress Interview, Physical, Bloodwork
2. Unstressed Cognitive Testing (Walter Reed)
3. Bicycle Exercise (graded) to 100 W for 3 minutes
4. Seated Lower Body Stress Testing to - 40 mmHg in 20 minutes
5. Poststress Monitoring, Blood and Urine Assays

Table I. Test Battery

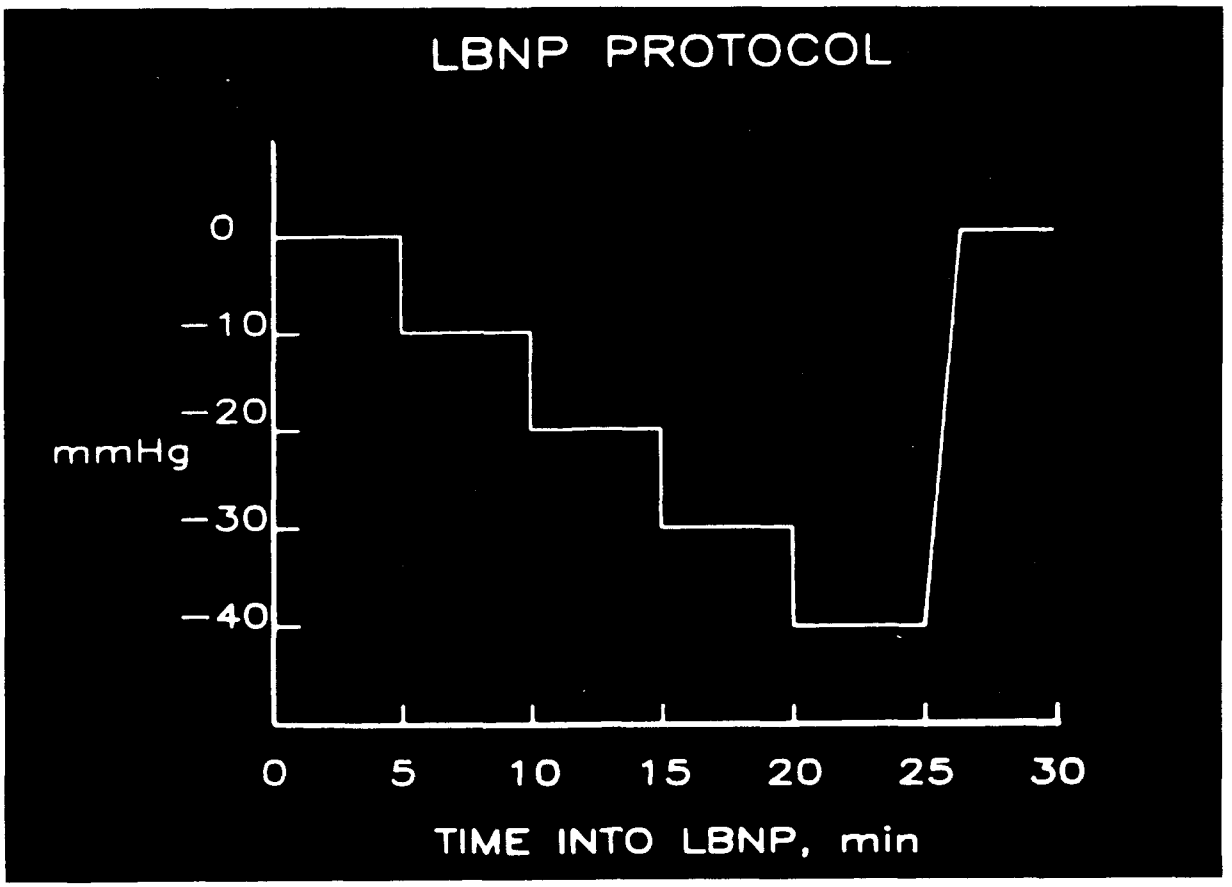

Figure 2. The lower negative pressure stress test is described in terms of the vacuum applied to the lower body as a function of time. The first 5 minutes were defined as a resting prestress measurement, and the ensuing 20 minutes were the stress protocol, and the final 5 minutes were a post test monitoring period.

responses per minute divided by the total number of minutes completed.

The third component consisted of bicycle exercise. Subjects performed seated bicycle exercise initiated at 50 watts, and then advanced to 75 and 100 watts at 3 minute intervals during hemodynamic monitoring.

The fourth component consisted of lower body negative pressure testing (LBNP).[23] This method was used to apply orthostatic stress to the subjects. The subject is sealed about the waist into a plethysmograph in a seated posture. Progressive vacuum can be applied, which results in blood pooling in the venous capacitance vessels of the lower extremities. This stress, if mild, simulates the stress of standing, and if greater, simulates the acceleration stress achieved in a human centrifuge.[24] After a 5 minute resting session, 10mmHg vacuum was applied to the lower extremities for the first 5 minutes, and then advanced to 20mmHg for the second 5 minutes (Figure 2).

The subsequent 5 minute periods had vacuums of 30 and 40mmHg. It was anticipated that the 40 mmHg vacuum would apply a total of +2G to the subject, when coupled with the 1G afforded by gravity alone. After the 20 minute LBNP protocol was complete, the vacuum was released to ambient conditions slowly over the ensuing 90 seconds. Endpoints for the stress test included the subject's request to terminate, significant bradycardia to rates less than 60 beats per minute, significant hypotension to blood pressures of 90/60 or lower, or evidence of impaired cerebral blood flow utilizing transcutaneous Doppler ultrasound.

Throughout the LBNP protocol, the subject repeated the computerized cognitive battery to examine the individual and combined effects of LBNP, beta-blockade, and altitude upon cognitive performance.

The fifth component of the test battery included post-stress monitoring. The subject was fitted with a 24-hour

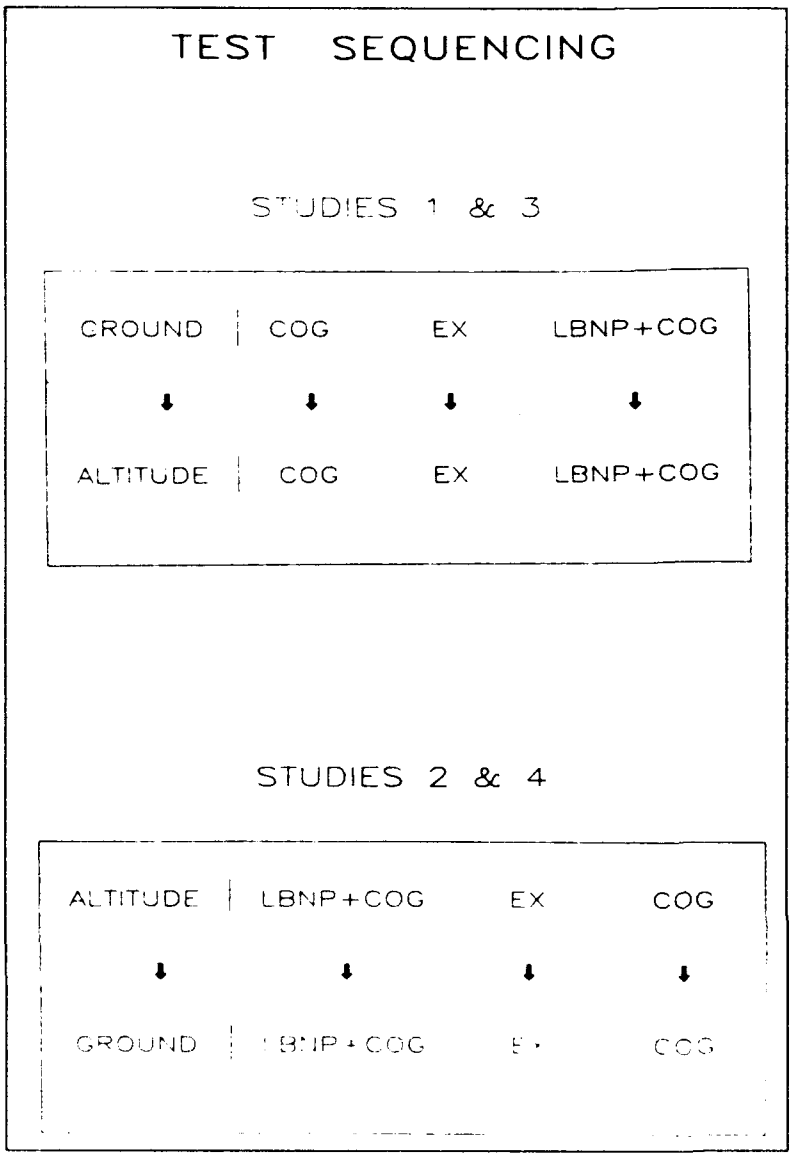

Figure 3. Schematic representation of test sequencing between studies 1 & 3, and 2 & 4. The arrows indicate the order of progression. COG=cognitive testing, EX=exercise testing, LBNP=lower body negative pressure testing.

ambulatory blood pressure monitor, which inflated every 15 minutes, affording up to 100 samples of systolic and diastolic pressure with heart rate in the 24-hour period.[25] In addition, the subject collected a 24-hour urine specimen for sodium and creatinine to assess hydration status.

The test battery, consisting of unstressed cognitive testing, exercise, and lower body negative pressure, was repeated at ground and at a simulated altitude of 12,500, utilizing a hypobaric chamber at the Civil Aeromedical Institute, Oklahoma City, Oklahoma. The test battery was administered on 4 occasions (Figure 3). On occasions 1 and 3, the sequence was ground and then altitude, with the battery sequence being unstressed cognitive, exercise, and lower body negative pressure. On testing days 2 and 4, the order was first altitude and then ground, with the battery protocol being lower body negative pressure, exercise, and unstressed cognitive testing. We did this because we felt that reversing the sequence of the stress orders would eliminate learning effects in the responses.

Instrumentation

Noninvasive hemodynamic monitoring was employed to ensure the safety of the test subject and to assess hemodynamic responses to the various stresses (Table II). The electrocardiogram was monitored in limb lead II utilizing a Hewlett Packard continuous monitor. The automated blood pressure cuff was inflated at least every 2 minutes to assess systolic (BPS), diastolic (BPD) and mean (BPM) blood pressure (Paramed 6300, Paramed Technology, Irvine, CA). Suprasternal transcutaneous Doppler ultrasound was employed to assess left ventricular function in terms of maximal ejection acceleration (MA), peak ejection velocity (PV), and stroke distance (SD) (Exerdop, Quinton Instruments, Seattle, WA).[26-28] Transthoracic bioimpedance techniques were utilized to determine stroke volume (SV), heart rate (HR), and cardiac output (NCCOM 3, BoMed Medical, Irvine, CA).[29-32]

The transthoracic impedance (TFI) reflected the electrolyte volume of the thorax.[33] To measure cerebral blood flow, transcutaneous pulsed Doppler ultrasonic measurements in the right middle cerebral artery were performed at rest, every 2 minutes into the LBNP stress protocol, and at peak tolerated stress. Measurements included peak systolic (Vs), diastolic (Vd), mean (Vm) and ratio (S/D) velocities (TC 64, Carolina Medical Electronics, King, NC).[34-36] The Doppler probe was held stationary in a helmet worn by the subject. All data but the transcranial monitoring were digitized and transmitted over an RS232 port to a host AT class personal computer for data logging and analysis in Lotus spreadsheets.

EKG		RATE & RHYTHM				HP
BP	BPS	BPD	BPM	HR		Paramed 9300
CO	SV	HR	LVET	TFI	EVI	BOMED NCCOM3
Qaorta	SV	MA	PV			QUINTON EXERDOP
Vmca	Vs	Vd	Vm	S/D		CME TC DOPPLER

Table II. Instrumentation

Statistical Methods

Statistical methods consisted of group means and standard deviations, with level of significance being established between group means using Student's t tests on paired or unpaired variables. Chi-square analysis established significance of treatment effects. Standard deviation (SD), and standard error of the mean (SEM) were calculated in the usual fashion.

Results

Tolerance

A total of 160 lower body negative pressure tests were performed, 80 at ground and 80 at altitude. In turn, 40 of the ground runs were done with subjects taking placebo, and 40 with atenolol. Correspondingly, at altitude 40 runs were done on beta-blockers and 40 on placebo. At ground, only 5 of the 80 lower body negative pressure tests were terminated for intolerance (Figure 4).

Intolerance was defined as declining blood pressure to levels below 90/60, declining heart rate to rates below 60, a drop in diastolic middle cerebral artery diastolic blood flow, or profound functional impairment. Only 2 of the 35 intolerant responses were terminated due to symptoms, and the remainder were terminated for hemodynamic compromise. Symptoms during intolerance included dizziness in 18, nausea in 18, lightheadedness in 11, epigastric fullness in 9, chest pressure in 4, loss of concentration in 10, and a distant, detached feeling in 9. Of the 5 intolerant runs at ground, all were associated with beta-blockade. The remaining 30 intolerant responses were observed at altitude. Of these 30 intolerant responses, 18 were observed with beta-blockade treatment, while 12 were observed with placebo treatment. The effect of altitude was significant ($P<.01$), and the effect of beta-blockade was significant ($P<.05$).

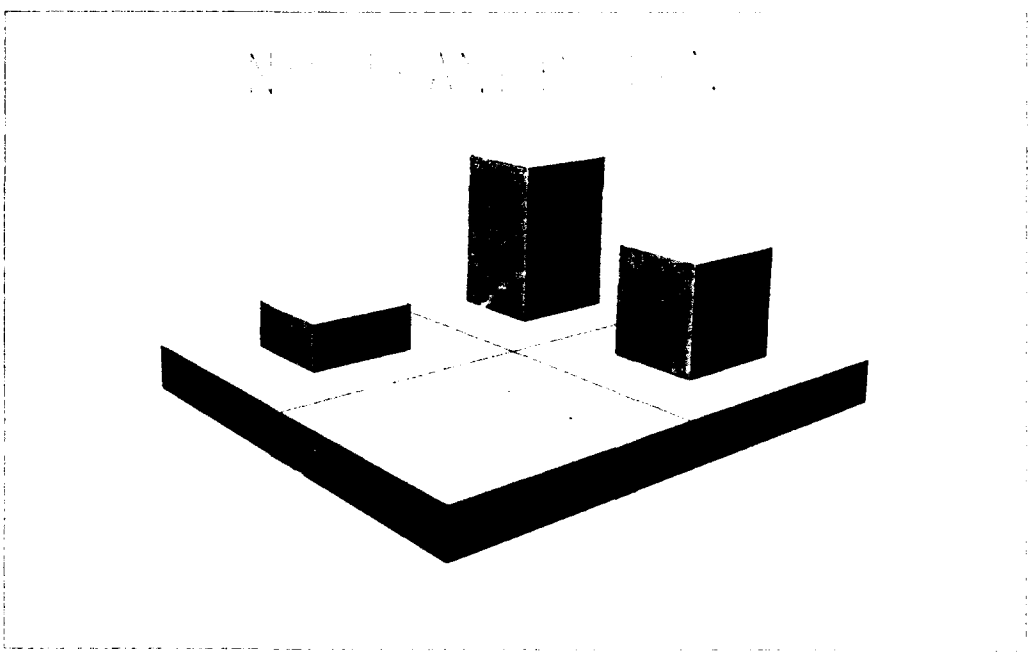

Figure 4. Graphical representation of intolerant responses, as influenced by ground or altitude conditions and placebo or beta-blocker treatment. Of 35 intolerant responses, 5 were experienced at ground on beta-blockade. Eighteen were experienced at altitude on beta-blockade, and 12 at altitude on placebo. No intolerant responses were observed at ground level testing during lower body negative pressure during placebo treatment.

	GROUND					
MEANS	N	HR	TFI	SV	MAP	SVR
TOL REST	75	73.40	33.80	84.30	98.00	1383
TOL PEAK	75	85.30	34.60	67.00	97.00	1511
INTOL REST	5	59.00	36.00	93.50	88.50	1322
INTOL PEAK	5	71.50	36.00	74.50	76.70	1020
PLACEBO REST	40	82.51	33.05	78.33	103.63	1406
PLACEBO PEAK	40	98.71	34.13	60.62	103.19	1534
BETA REST	40	62.30	34.88	91.18	90.75	1361
BETA PEAK	40	69.95	35.59	74.77	88.66	1452
STD DEV	N	HRSD	TFISD	SVSD	MAPSD	SVRSD
TOL REST	75	15.70	8.00	20.70	11.70	325.0
TOL PEAK	75	20.00	5.70	19.30	19.00	431.0
INTOL REST	5	5.80	4.80	18.60	8.90	229.0
INTOL PEAK	5	7.10	4.50	12.00	7.70	328.0
PLACEBO REST	40	15.83	5.31	21.49	11.61	36.58
PLACEBO PEAK	40	18.28	5.33	18.86	17.11	48.16
BETA REST	40	7.83	5.88	22.00	9.47	31.76
BETA PEAK	40	7.17	5.70	18.92	12.44	39.42
	ALTITUDE					
MEANS	N	HR	TFI	SV	MAP	SVR
TOL REST	50	76.70	31.30	92.70	98.70	1289
TOL PEAK	50	87.30	32.60	77.70	95.70	1420
INTOL REST	30	78.00	29.20	90.90	95.80	1177
INTOL PEAK	30	79.70	28.30	98.30	77.00	949
PLACEBO REST	40	87.76	29.97	83.78	103.40	1294
PLACEBO PEAK	40	97.86	30.21	75.77	93.87	1182
BETA REST	40	66.60	31.09	100.09	92.40	1203
BETA PEAK	40	70.73	30.91	95.11	84.04	1113
STD DEV	N	HRSD	TFISD	SVSD	MAPSD	SVRSD
TOL REST	50	14.30	6.00	26.00	12.70	390.0
TOL PEAK	50	18.00	6.10	23.00	12.50	364.0
INTOL REST	30	13.30	5.90	21.00	12.70	325.0
INTOL PEAK	30	15.00	5.90	30.00	12.30	247.0
PLACEBO REST	40	13.44	6.24	28.68	12.45	50.19
PLACEBO PEAK	40	17.14	6.34	34.30	16.43	44.52
BETA REST	40	6.51	6.51	26.37	10.62	38.44
BETA PEAK	40	5.66	7.37	27.46	12.97	44.94

Table III. Summary of Hemodynamic Responses During LBNP. (Sorted By Treatment Tolerance.)

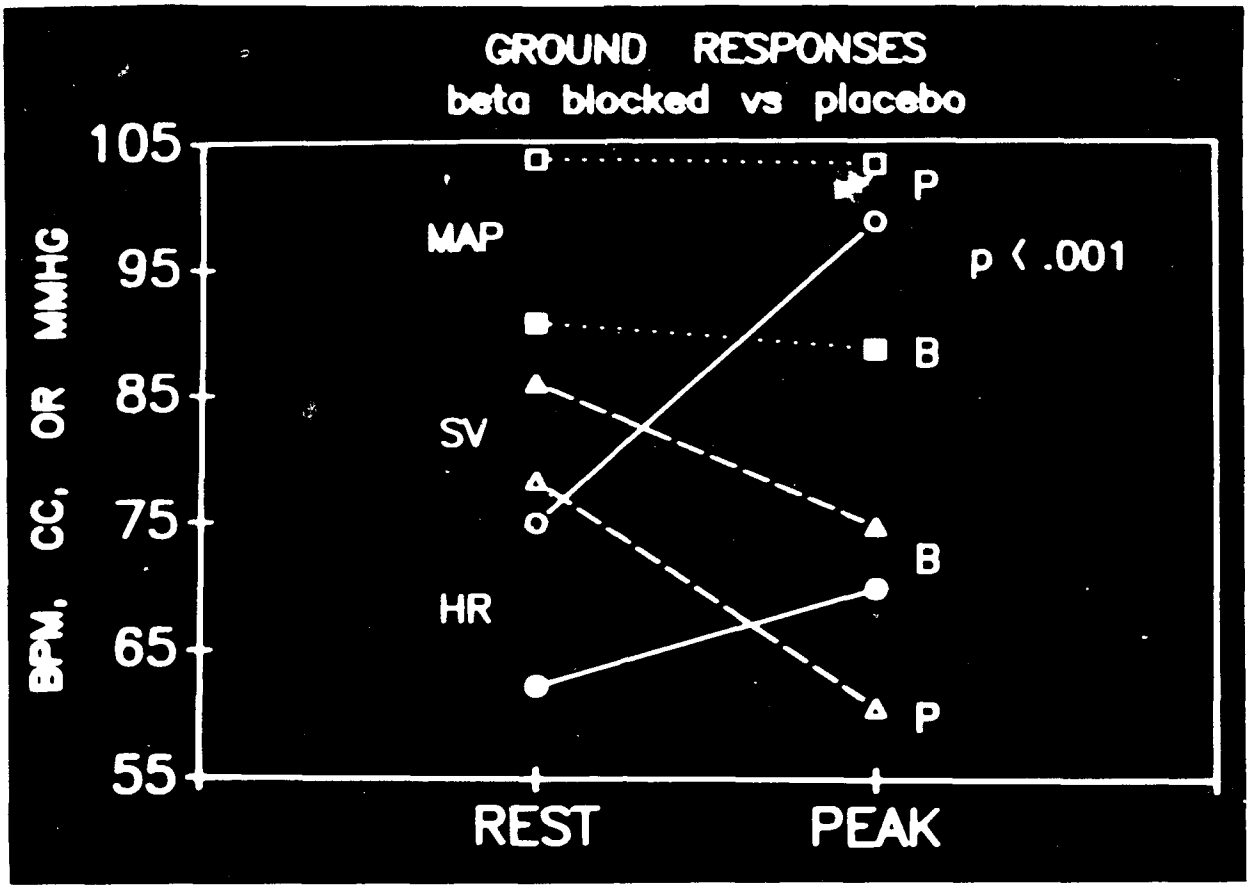

Figure 5. Responses of mean arterial pressure (MAP:squares), stroke volume (SV:triangles), and heart rate (HR:circles) between rest and peak tolerated lower body negative pressure for placebo (P) and beta-blocker (B) treatment groups at ground. The lower body negative pressure stress augmented heart rate significantly (P < .001) in the placebo treated group compared to the beta-blocked group.

Hemodynamic Responses (Table III)

A. Beta-blockade versus Placebo (Figures 5 & 6)

Before the initiation of lower body negative pressure, beta-blocker subjects had lower heart rates (62 + 7.8 vs 82 + 15.8, P < .001), mean arterial pressure (91 + 9.5 vs 104 + 11.6, P < .001), and higher bioimpedance stroke volume (91 + 22 vs 78 + 21, P=ns), as compared to placebo treated subjects (n=40). At the end of lower body negative pressure, heart rates (70 + 7 vs 99 + 18, P < .001) and mean arterial pressures (89 + 12 vs 103 + 17, P < .001) were lower and stroke volumes (74 + 19 vs 61 + 19, P=ns) were higher compared to placebo treatment.

The stress-induced rise in heart rate was lower in the beta-blocker subjects. Both beta-blocker and control subjects manifested a decrement in mean arterial pressure with lower body negative pressure, and the degree of decrement was not significant between the 2 treatments. Stroke volume declined proportionally in both the beta-blocker and placebo groups. Systemic vascular resistance, defined as 80 times the mean arterial pressure divided by the cardiac output, was similar in both groups at rest (1,368 + 317 vs 1,418 + 365, P=ns).

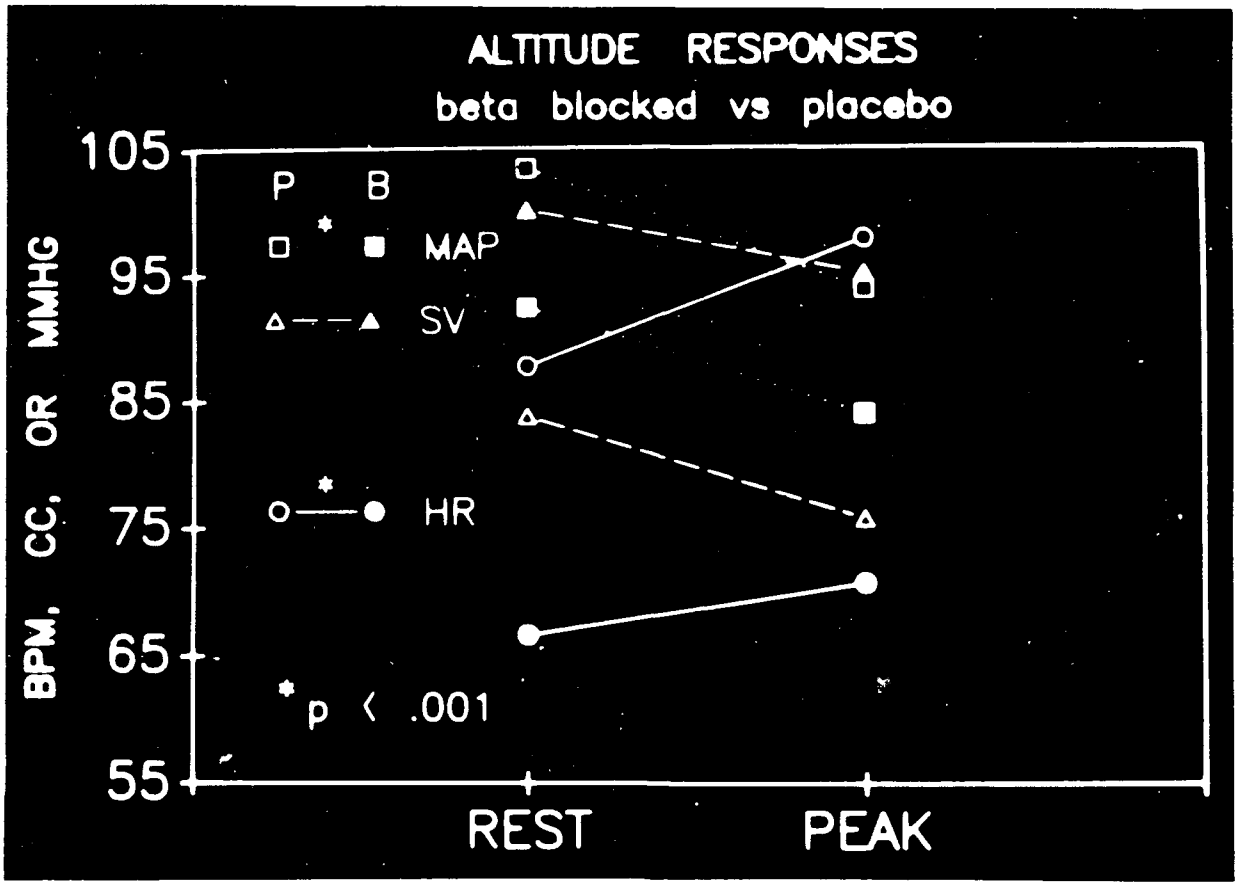

Figure 6. The hemodynamic descriptors MAP, SV, and HR are plotted between rest and peak tolerated lower body negative pressure while at a simulated altitude of 12,500 feet. Means are plotted. Placebo treated responses are compared to beta blocked responses. Beta-blocked patients had significantly lower mean arterial pressure and heart rate at rest and peak tolerated LBNP (P < .001).

Both beta-blocker and placebo-treated subjects augmented systemic vascular resistance during lower body negative pressure, with values rising to 1,534 + 481 in the placebo group versus 1,458 + 394 in the beta-blocker group. These differences were not statistically significant (Figure 7).

Thus, the minus 40 mmHg seated lower body negative pressure stress test induced typical physiologic responses to orthostatic stress in the subjects, with decrements in mean arterial pressure and stroke volume, accompanied by a rise in heart rate.[37-43]

The only significant beta-blocker effect seen at ground lower-body negative pressure stress testing was the blunted rise in heart rate. This appeared to be offset by a higher stroke volume at any given level of lower body negative pressure stress, such that adequate cardiac output and systemic vascular resistance were maintained.[10,11]

As already mentioned, 30 of the 80 lower body negative pressure runs at altitude were complicated by intolerance. Since the majority of these responses, which are characterized by hypotension and bradycardia, are in the beta-blocker group, the intolerant physiologic state heavily biases the group altitude data.

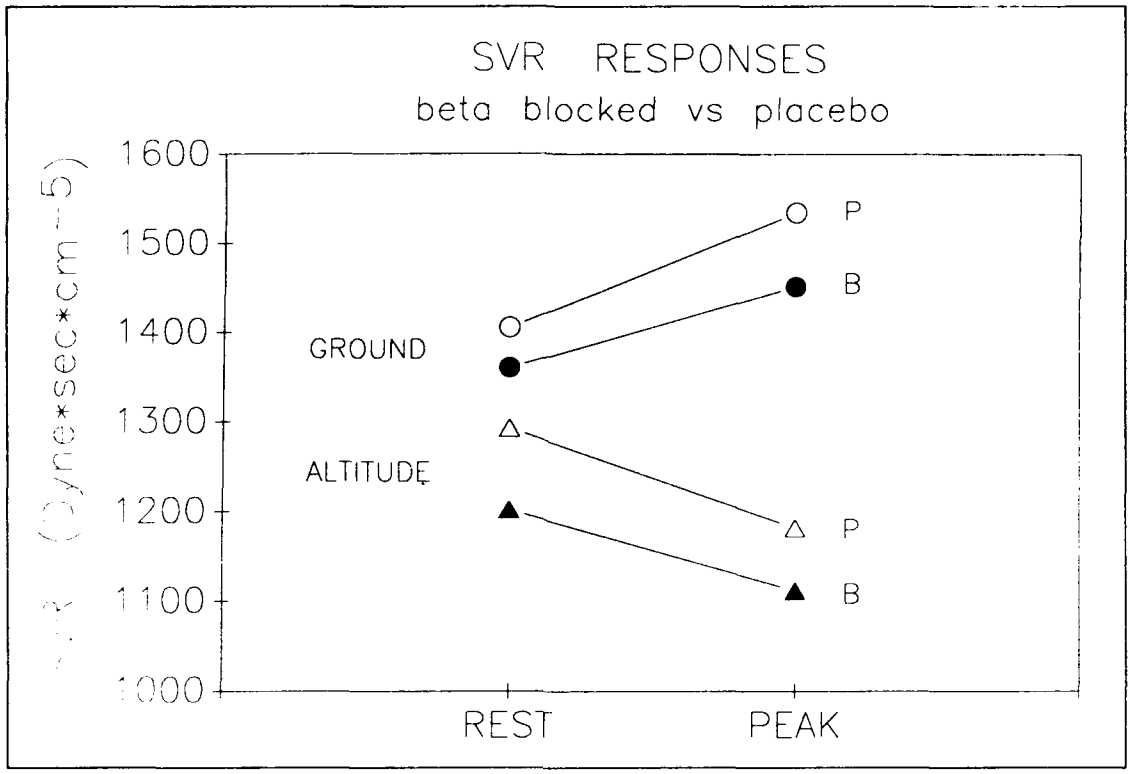

Figure 7. Group mean systemic vascular resistance (SVR) responses are plotted between rest and peak lower body negative pressure at ground and at altitude. Both placebo and beta-blocked subjects had a rise in systemic vascular resistance between rest and peak tolerated lower body negative pressure at ground, but at altitude the resistance fell (P=ns).

At altitude, resting values for heart rate were higher in both beta-blocker and placebo-controlled subjects, compared to those at ground (62 + 7.8 and 82 + 15.8 vs 67 + 6.5 and 88 + 13.4, P=ns both). Values for mean arterial pressure were similar to ground measurement (91 + 9.5 and 104 + 11.6 vs 92 + 10.6 and 103 + 12.5). Stroke volume values were higher at altitude for both groups, compared to stroke volume at ground (74 + 19 and 61 + 19 vs 100 + 26 and 84 + 27, P < .001 both).

As a result, systemic vascular resistance was lower at altitude for both groups, compared to ground measurements (1,368 + 317 and 1,418 + 365 vs 1,203 + 384 and 1,294 + 502, P=ns both). With the stress of lower-body negative pressure, the placebo-treated group had a rise in heart rate (88 + 13.4 to 98 + 17.1, P=ns), a fall in mean arterial pressure (103 + 12.5 to 94 + 16.4, P=ns), and a fall in stroke volume (84 + 27 to 76 + 34, P=ns). These parameters caused an insignificant decline in systemic vascular resistance to peak tolerated lower body negative pressure; and this peak value was lower than corresponding measurements at ground (1,294 + 502 to 1,182 + 445, P=ns). Beta-blocked responses showed similar trends in heart rate (66 + 6.5 to 71 + 5.7, P=ns), arterial pressure (92 + 10.6 to 84 + 13.0, P=ns), stroke volume (100 + 26.4 to 95 + 27, P=ns) and vascular resistance (1,203 + 384 to 1,113 + 449, P=ns). Heart rate and pressure data were significantly lower at peak LBNP for beta-blocker vs. placebo subjects (P < .001).

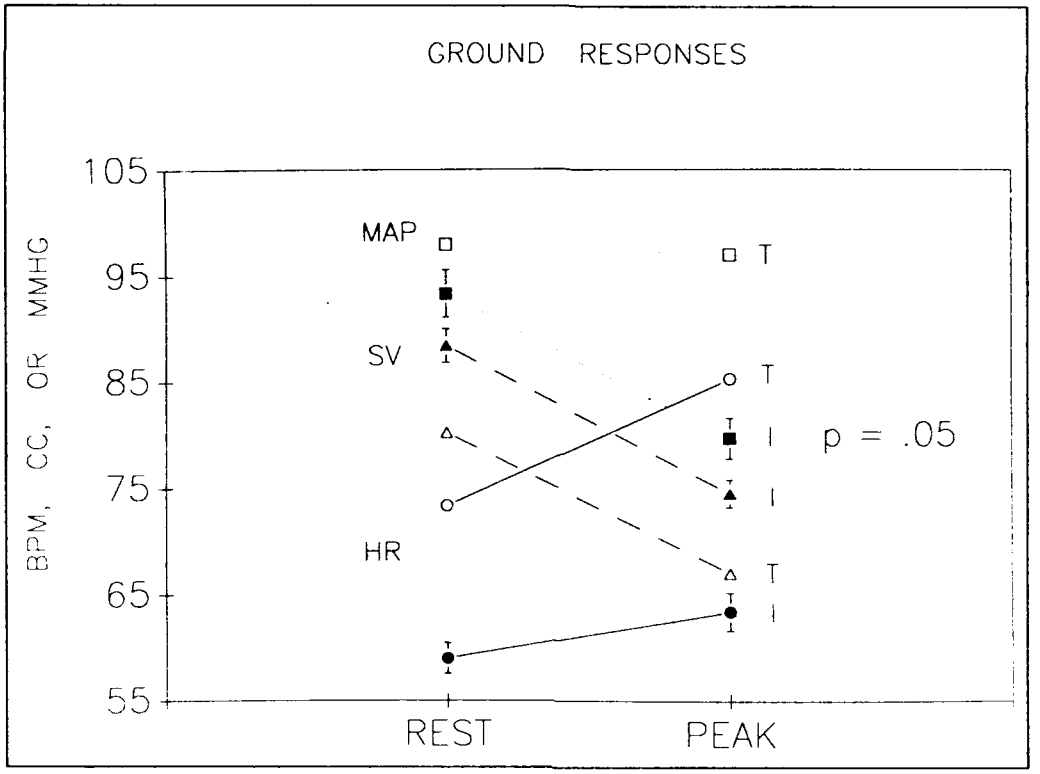

Figure 8. Hemodynamic parameters MAP, SV, and HR are plotted between rest and peak tolerated lower body negative pressure at ground. Subject responses are stratified on the basis of tolerance (T) or intolerance (I) to lower body negative pressure. The intolerant fall in MAP at ground was significant (P < .05).

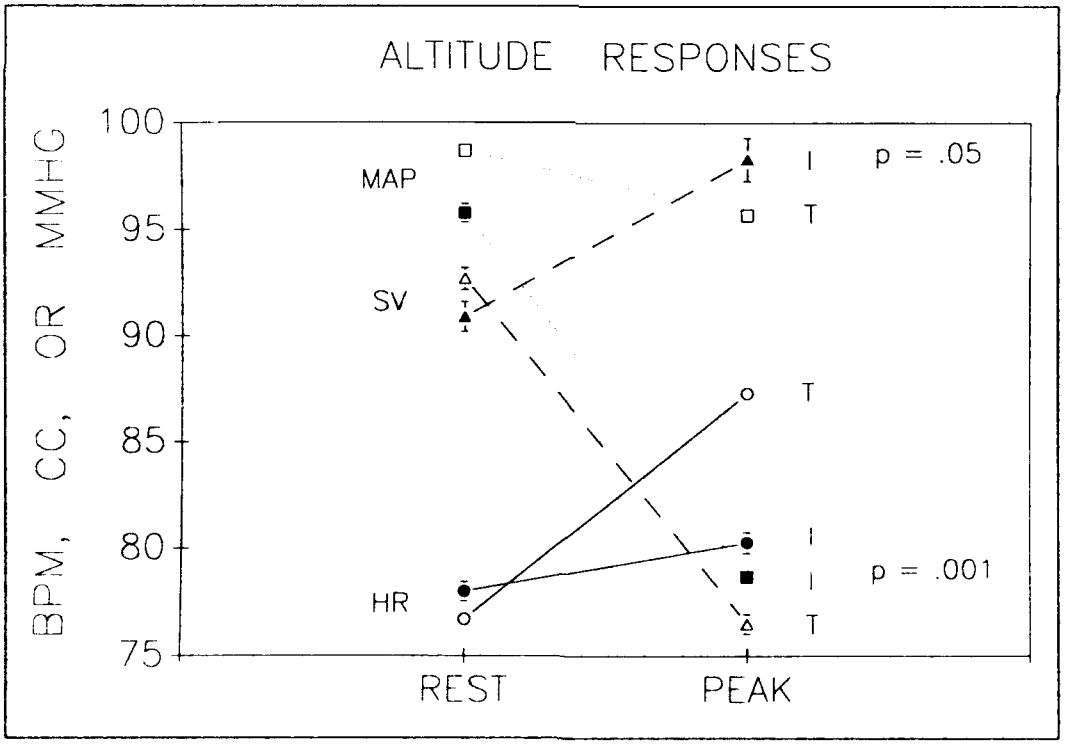

Figure 9. Hemodynamic responses MAP, SV, and HR are plotted between rest and peak tolerated lower body negative pressure administered at altitude. Tolerant (T) and intolerant (I) responses are illustrated. Altitude intolerant responses were marked by a significant (P < .001) fall in mean arterial pressure (squares) and rise in stroke volume (triangles) (P < .05) at the point of intolerance to lower body negative pressure.

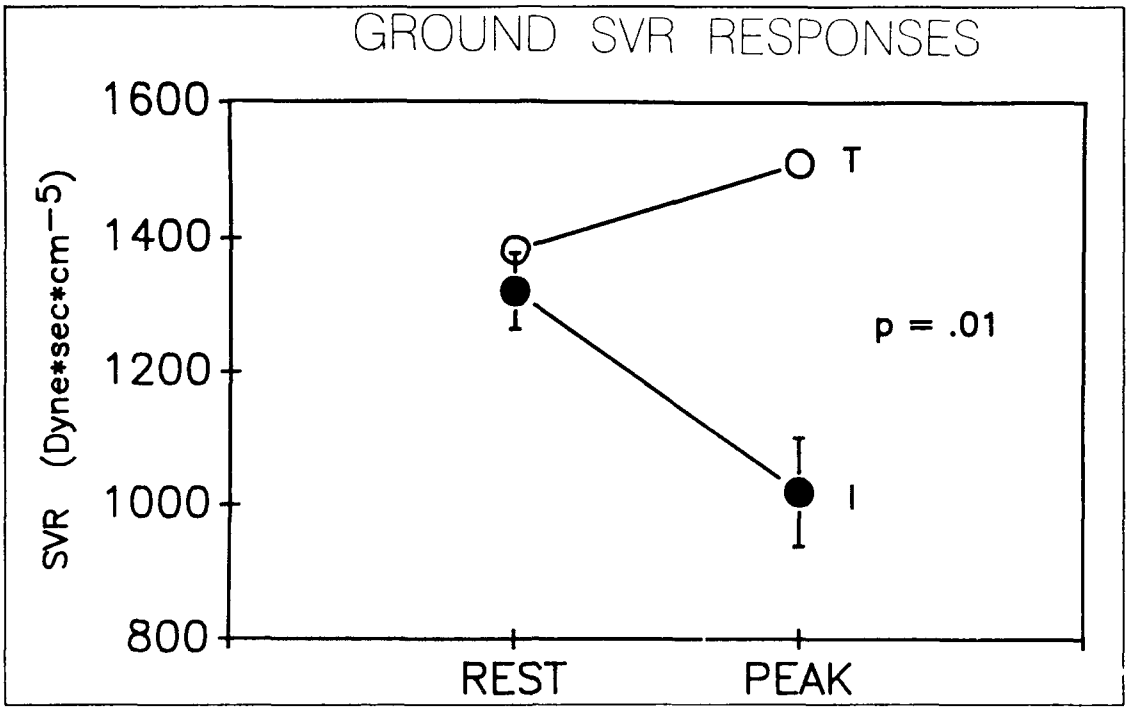

Figure 10. Systemic vascular resistance responses between rest and peak tolerated lower body negative pressure for intolerant (I) and tolerant (T) subjects. The intolerant response was marked by significant depression in systemic vascular resistance in response to orthostatic stress (P < .01).

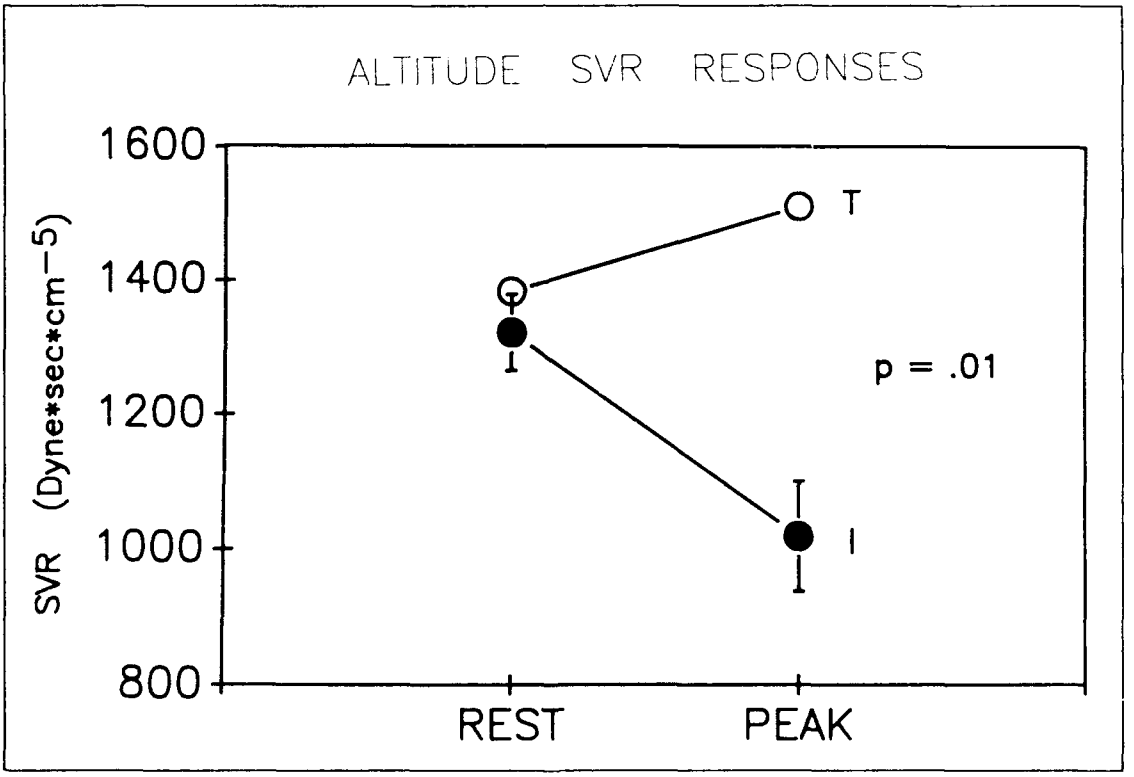

Figure 11. Responses of systemic vascular resistance between rest and peak tolerated lower body negative pressure for tolerant (T) and intolerant (I) subjects tested at altitude. Intolerance was marked by a significant decline in systemic vascular resistance between rest and peak tolerated lower body negative pressure (P < .01).

MEANS		**REST**			**EXERCISE**			
	N	HR	BPS	BPD	HR	BPS	BPD	RPP
GROUND								
BETA	40	60.46	124.10	79.08	102.36	156.56	84.97	166.72
PLACEBO	40	77.68	137.63	90.00	126.63	182.83	92.83	230.68
ALTITUDE								
BETA	40	68.15	123.03	79.41	106.90	156.62	79.77	168.77
PLACEBO	40	86.75	138.40	89.15	134.15	186.23	83.30	248.93
STANDARD DEVIATIONS								
GROUND								
BETA	40	12.08	14.85	11.49	11.21	21.07	18.35	35.00
PLACEBO	40	16.94	16.27	12.78	17.87	26.16	14.25	58.46
ALTITUDE								
BETA	40	9.54	16.02	11.99	13.71	29.35	16.90	60.96
PLACEBO	40	19.90	17.45	13.46	17.90	18.03	15.03	46.26

Table IV. Exercise at Ground and Altitude.

B. Tolerant versus Intolerant Responses (Figures 8 & 9)

Only 5 of the 80 lower body negative pressure testing runs at ground were complicated by intolerance, and all 5 intolerant runs were associated with beta-blockade. Since intolerance was uniformly associated with beta-blockade, it is not surprising that heart rate responses between rest and peak LBNP at ground were blunted in the intolerant subjects, compared to tolerant subjects (59 + 5.8 to 71 + 7.1 vs 73 + 15.7 to 85 + 20.0, P=ns). Likewise, mean arterial pressure fell to a greater degree during LBNP stress in the intolerant subjects, compared to tolerant subjects (88.5 + 8.9 to 76.7 + 7.7 vs 98 + 11.7 to 97 + 19, $P < .05$). Stroke volume fell in both groups, and the difference between intolerant and tolerant subjects was insignificant (93.5 + 18.6 to 74.5 + 12 vs 84.3 + 20.7 to 67 + 19.3). Systemic vascular resistance (Figure 10) increased in tolerant subjects, and decreased in intolerant subjects with increasing lower-body negative pressure (1,383 + 325 to 1,511 + 431 vs 1,322 + 229 to 1,020 + 328, $P < .01$). In summary, intolerance at ground during beta-blockade was most associated with an impaired rise in heart rate and progressive peripheral vasodilation in response to the orthostatic stress. These responses are comparable to intolerant responses at altitude.

Compared to ground, both tolerant and intolerant subjects had higher heart rates resting at altitude (76.6 + 14.3 and 78 + 13.3 vs 73.4 + 15.7 and 59 + 5.8, P=ns). Similar insignificant differences were returned for mean arterial pressure and stroke volume. With lower-body negative pressure, tolerant subjects showed a slightly exaggerated rise in heart rate (76.7 + 14.3 to 87.3 + 18.0, $P < .05$), fall in mean arterial pressure (98.7 + 12.7 to 95.7 + 12.5, P=ns), and fall in stroke volume (92.7 + 26 to 77.7 + 23, $P < .05$), compared to ground level testing. As a result, systemic vascular resistance (Figure 11) rose in tolerant subjects between rest and peak tolerated lower-body negative pressure (1,289 + 390 to 1,420 + 364, P=ns). In contradistinction, intolerant subjects had a blunted rise in heart rate (78 + 133 to 79.7 + 15), a significant fall in mean arterial pressure (95.8 + 12.7 to 77 + 12.3, $P < .001$), and a paradoxical rise in stroke volume (90 + 21 to 98.3 + 30, P=ns) between restand peak tolerated lower body negative pressure. Examining individual alterations in stroke volume, the response of intolerant subjects to increasing lower body negative pressure was a progressive decrement in systemic vascular resistance, culminating in a vascular resistance much lower at peak LBNP than it was at rest (1,177 + 325 to 949 + 247, $P < .05$).

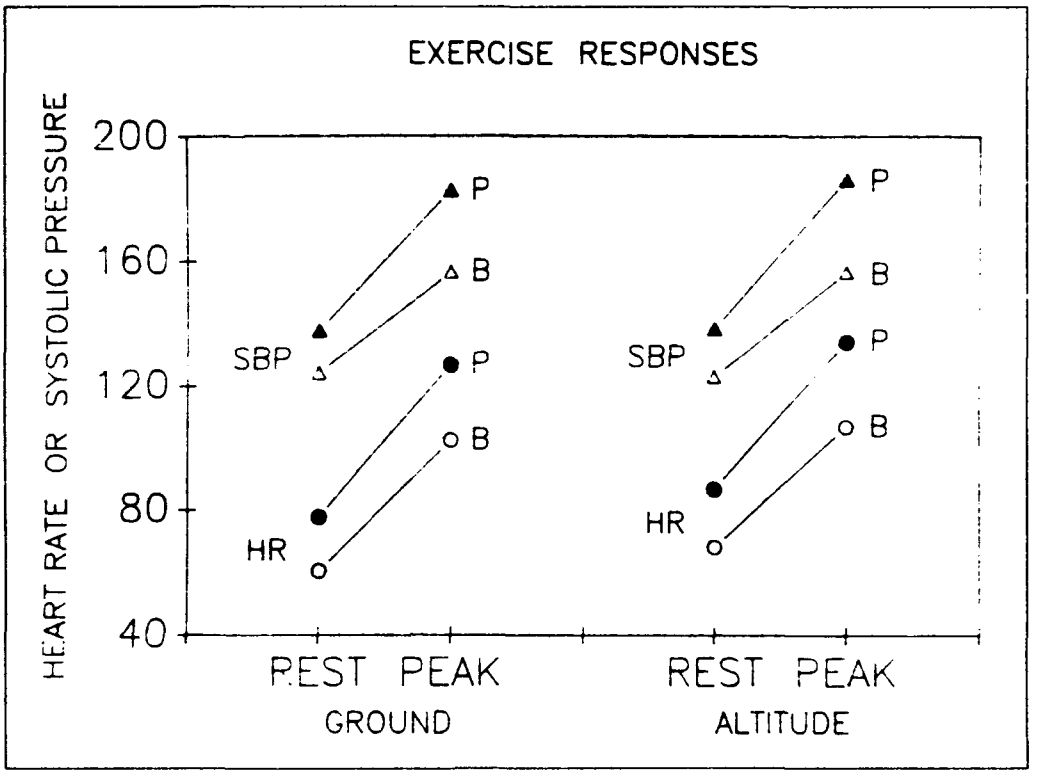

Figure 12. Exercise performance of placebo treated and beta-blocked subjects between rest and peak exercise at ground and at a simulated altitude of 12,500 feet. Means are plotted for heart rate (HR) and systolic blood pressure (SBP) during the various test conditions.

Exercise Responses (Table IV, Figure 12)

A. Beta-Blockade vs. Placebo

All subjects were capable of pedaling to 100 watts for 3 minutes on the seated bicycle at ground and at altitude. At ground, heart rates were significantly lower in the beta-blocked subjects at rest (60 + 12.1 vs 78 + 16.9, P < .001), and at peak exercise (102 + 11.2 vs 126 + 17.9, P < .001) compared to placebo treated subjects. In addition, systolic blood pressures were lower at rest (124 + 14.9 vs 137 + 16.3, P<.04), and at peak exercise (156 + 21.1 vs 183 + 26.2, P<.01).

As a result, beta-blocked subjects had lower rate-pressure products, calculated as HR X SBP/100, at peak exercise than their placebo-treated counterparts (166 + 35 vs 231 + 58.5, P < .001). At altitude, resting heart rates were higher compared to ground prior to exercise (68 + 9.5 and 87 + 19.9, both P=ns), but systolic blood pressures were similar. Both placebo and beta-blocked subjects achieved similar rate pressure products at peak exercise at altitude compared to ground (249 + 46 vs 169 + 35). Rate-pressure products were significantly lower in beta-blocker subjects (P <. 01).

B. Tolerance vs Intolerance

At ground, resting values for heart rate and systolic blood pressure were similar in tolerant and intolerant groups (73.7 + 18.3 vs 70 + 14.5). With exercise, systolic pressure (132.9 + 17.4 and 123.2 + 15.8 to 171.5 + 28.9 and 167.7 + 23.1) and heart rate (to 118.2 + 21 and 115 + 18.2) rose in both groups, with differences being insignificant. The peak double product achieved in intolerant and tolerant subjects exercising at ground to 100 watts was not significantly different (206.6 + 65 vs 195.2 +52).

LBNP MIN	TOLERANT GROUP, N=50 MEANS MV	S/D	PV	DV	INTOLERANT GROUP, N=30 MEANS MV	S/D	PV	DV
REST	54.05	2.08	85.58	41.80	56.75	2.03	88.53	44.12
7	53.63	2.13	85.00	40.91	53.10	2.13	85.68	41.68
12	51.95	2.11	82.11	39.97	52.24	2.09	84.45	40.97
17	49.42	2.10	78.32	37.97	48.07	2.28	81.21	37.52
22	47.32	2.07	75.71	37.51	42.95	2.32	78.56	33.59
	STANDARD DEVIATIONS				STANDARD DEVIATIONS			
LBNP MIN	MV	S/D	PV	DV	MV	S/D	PV	DV
REST	11.91	0.25	17.49	9.85	10.53	0.20	16.44	8.99
7	13.45	0.34	19.03	11.15	12.80	0.35	17.15	11.73
12	14.29	0.30	20.01	11.87	10.55	0.24	14.79	8.87
17	13.11	0.28	18.08	10.16	12.23	0.53	15.28	11.24
22	12.29	0.31	17.75	10.91	11.92	0.38	10.99	11.59

Table V. Transcranial Monitoring at Altitude During LBNP.

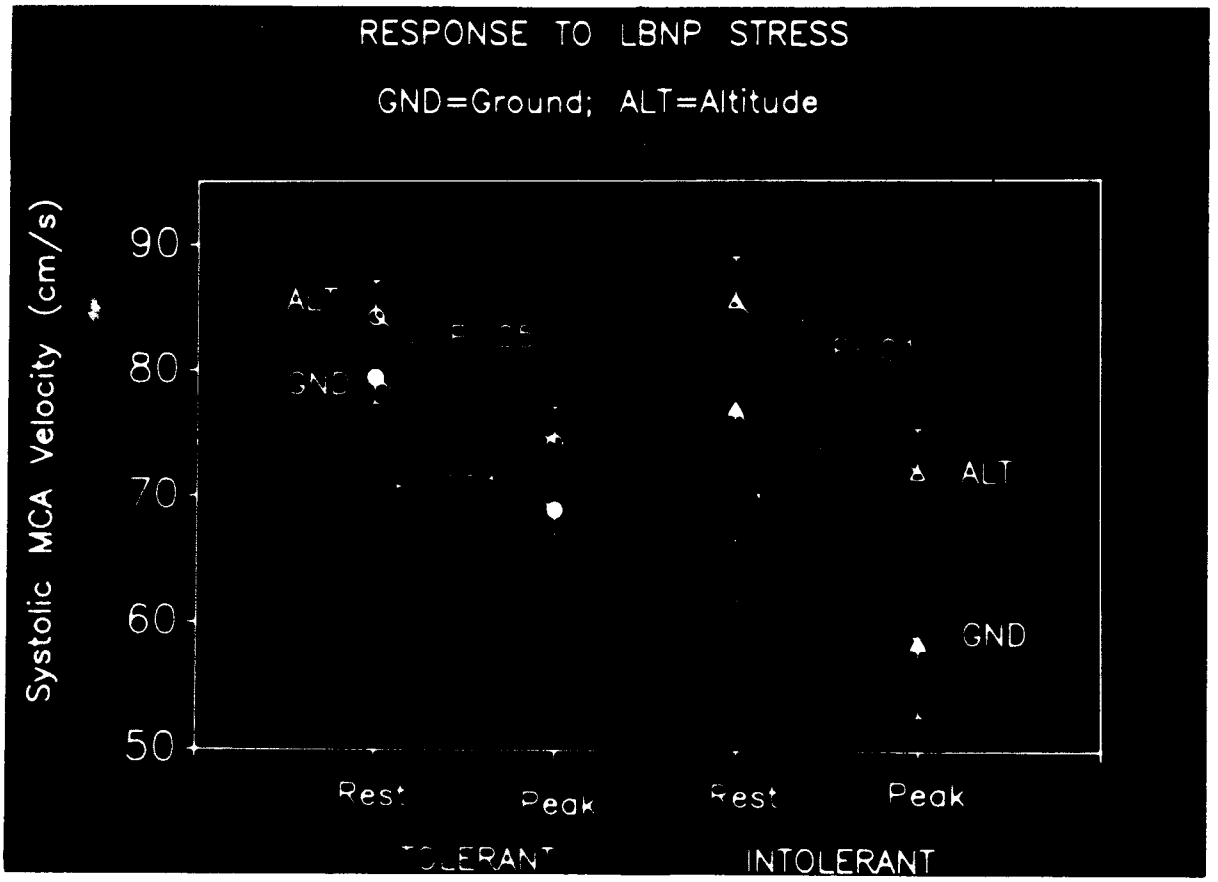

Figure 13. Transcranial Doppler monitoring of the systolic middle cerebral artery flow velocity (MCA) in subjects tolerant and intolerant to lower body negative pressure between rest and peak LBNP effect, at ground (GND) and altitude (ALT).

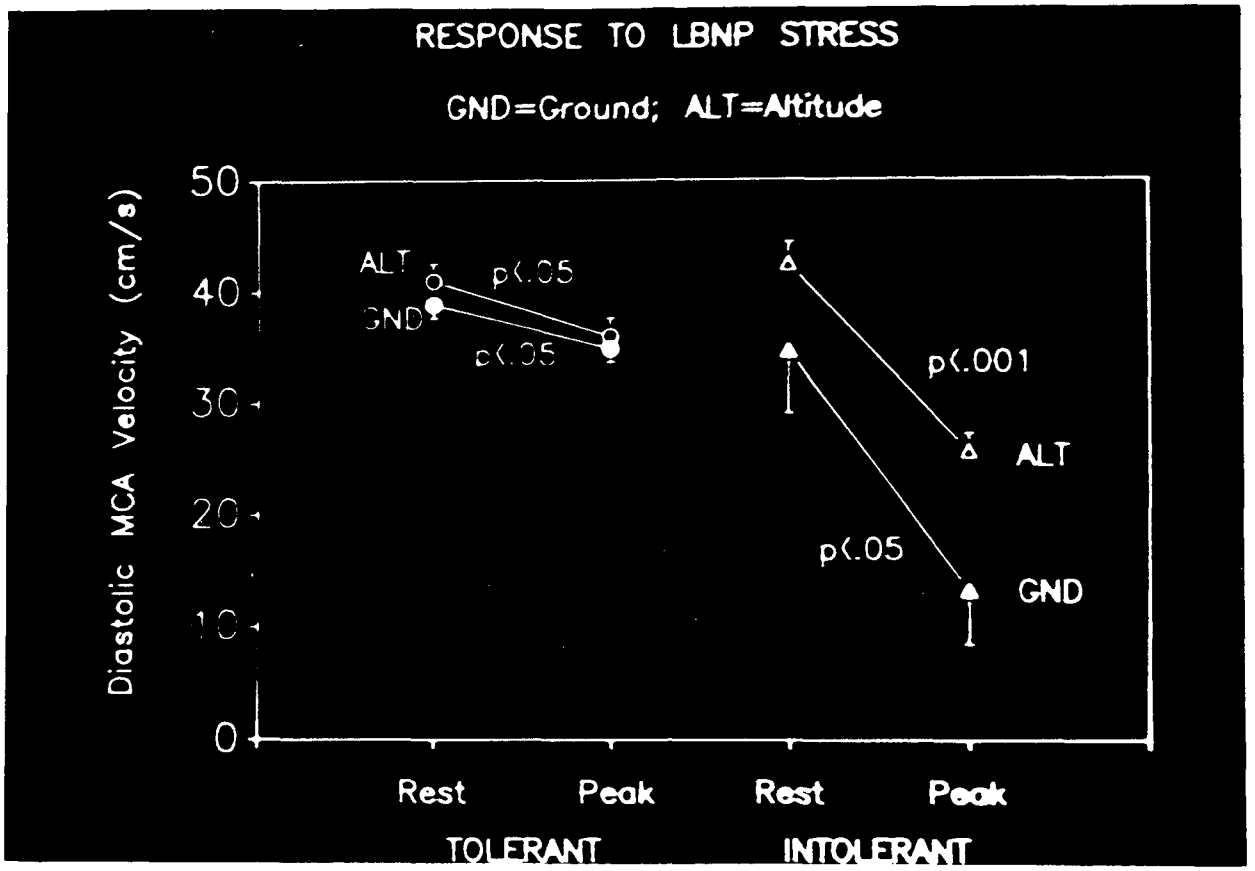

Figure 14. Plots of diastolic middle cerebral artery flow velocity between rest and peak LBNP at ground and altitude in tolerant and intolerant subjects.

At altitude, tolerant and intolerant subjects had similar resting heart rates (84 + 17 vs 72 + 15, P=ns) and systolic blood pressures (133 + 17.4 vs 125 + 18.2, P=ns). At peak exercise, significant differences were found between heart rates (136 + 18.7 vs 111 + 14.2, P < .001), and systolic blood pressure (190 + 22 vs 156 + 27, P < .001) in tolerant and intolerant subjects, probably reflecting the prevalence of beta-blockers in the intolerant group.

Transcranial Doppler Responses (Table V)

A. Tolerance to lower body negative pressure

The transcranial Doppler flow velocity in the middle cerebral artery was indexed by the peak systolic velocity (Figure 13), diastolic velocity (Figure 14), the mean velocity (Figure 15), and the systolic to diastolic velocity ratio (Figure 16).

These 4 parameters were measured at rest and at 2 minute intervals as lower body negative pressure progressed.

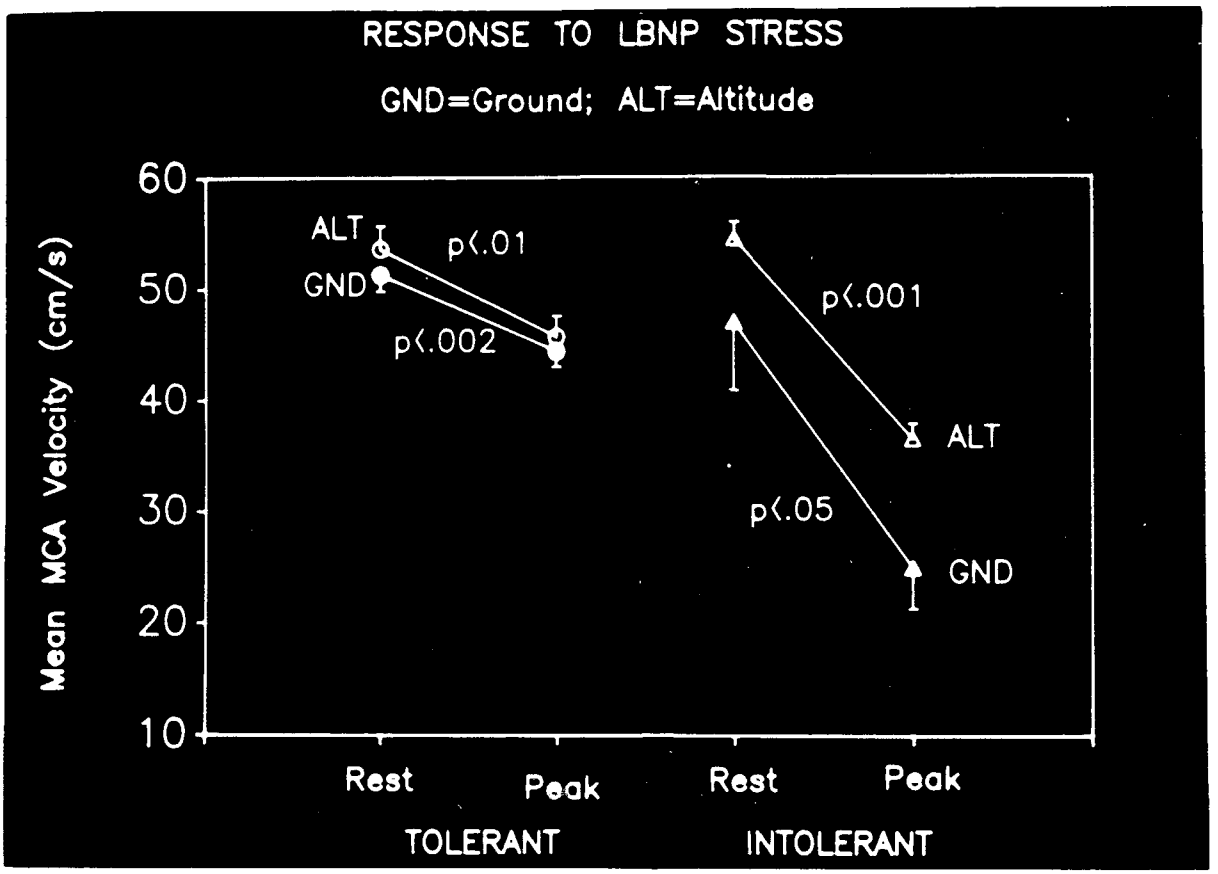

Figure 15. Plots of mean middle cerebral artery flow velocity between rest and peak tolerated lower negative pressure at ground and altitude in tolerant and intolerant subjects.

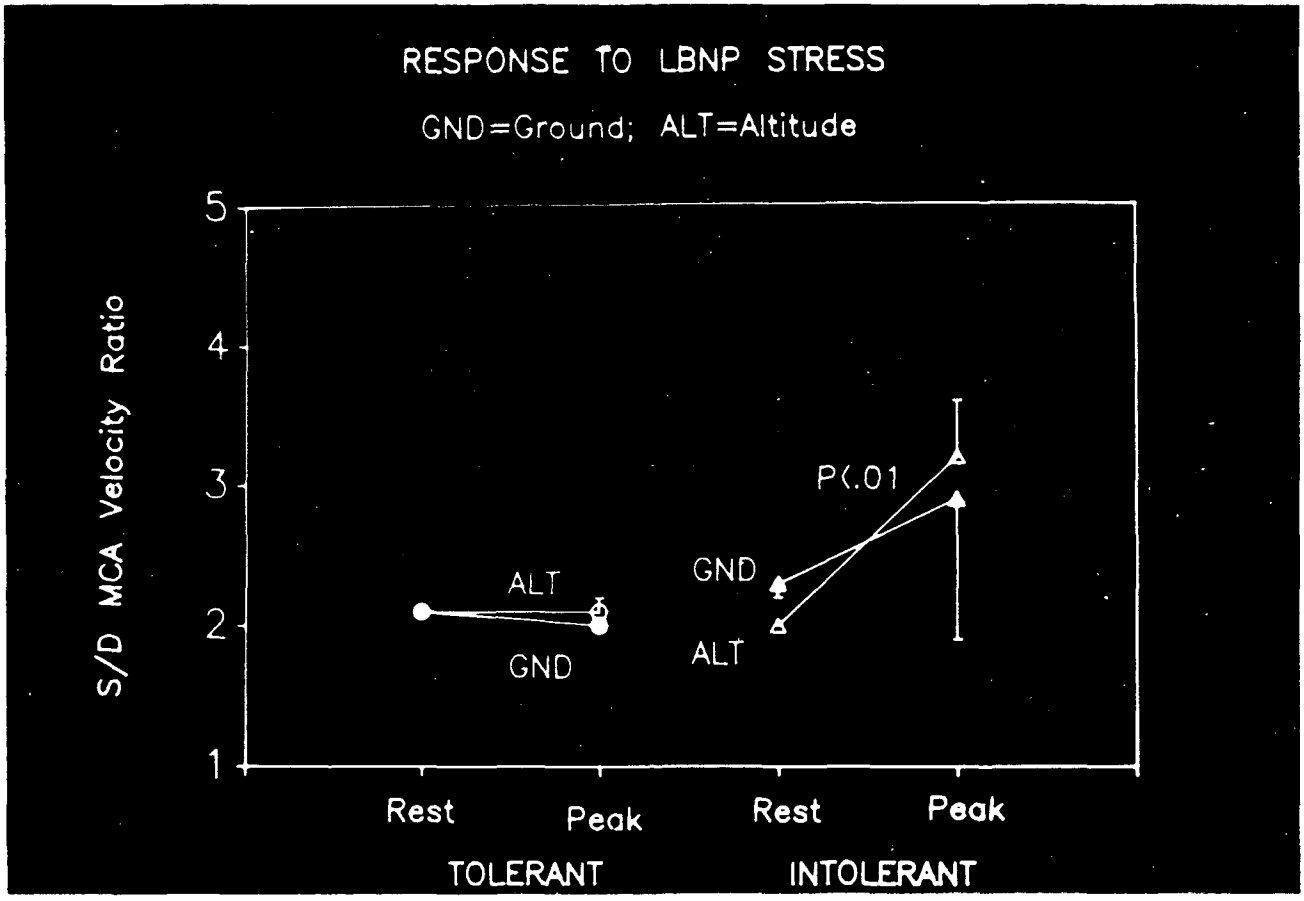

Figure 16. Plots of the systolic-to-diastolic middle cerebral artery flow velocity ratio between rest and peak tolerated lower body negative pressure at altitude and ground in tolerant and intolerant subjects.

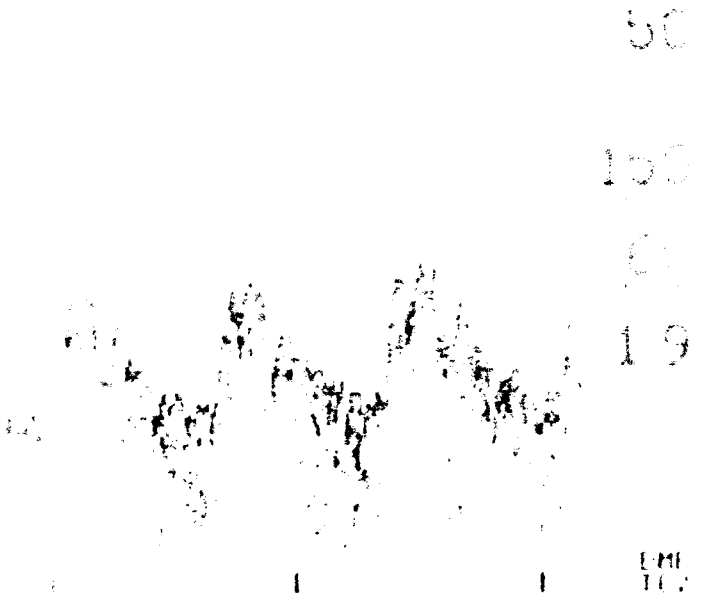

Figure 17. Transcranial monitoring of middle cerebral flow velocity during a tolerant response to lower body negative pressure. Minus 40 mmHg lower body negative pressure (photo on right) produced an increase in the heart rate, and a decrement in Doppler systolic and diastolic velocity, but the systolic-to-diastolic ratio was unchanged.

Figure 17 demonstrates a characteristic tolerant subject tracing. In tolerant subjects, the systolic velocity decreased from rest to peak orthostatic stress (85.6 + 17.5 to 75.7 + 17.8 cm/s, P=ns).

The diastolic velocity also decreased in response to orthostatic stress (41.8 + 9.9 to 37.5 + 10.9 cm/s P=ns). A minor, and insignificant decrease in mean flow velocity, which correlates with cerebral blood flow, was observed (54 + 12 to 47.3 + 12.3 cm/s). The systolic-to-diastolic (S to D) ratio remained constant between rest and peak orthostatic stress (2.08 + 0.25 to 2.07 + .31).

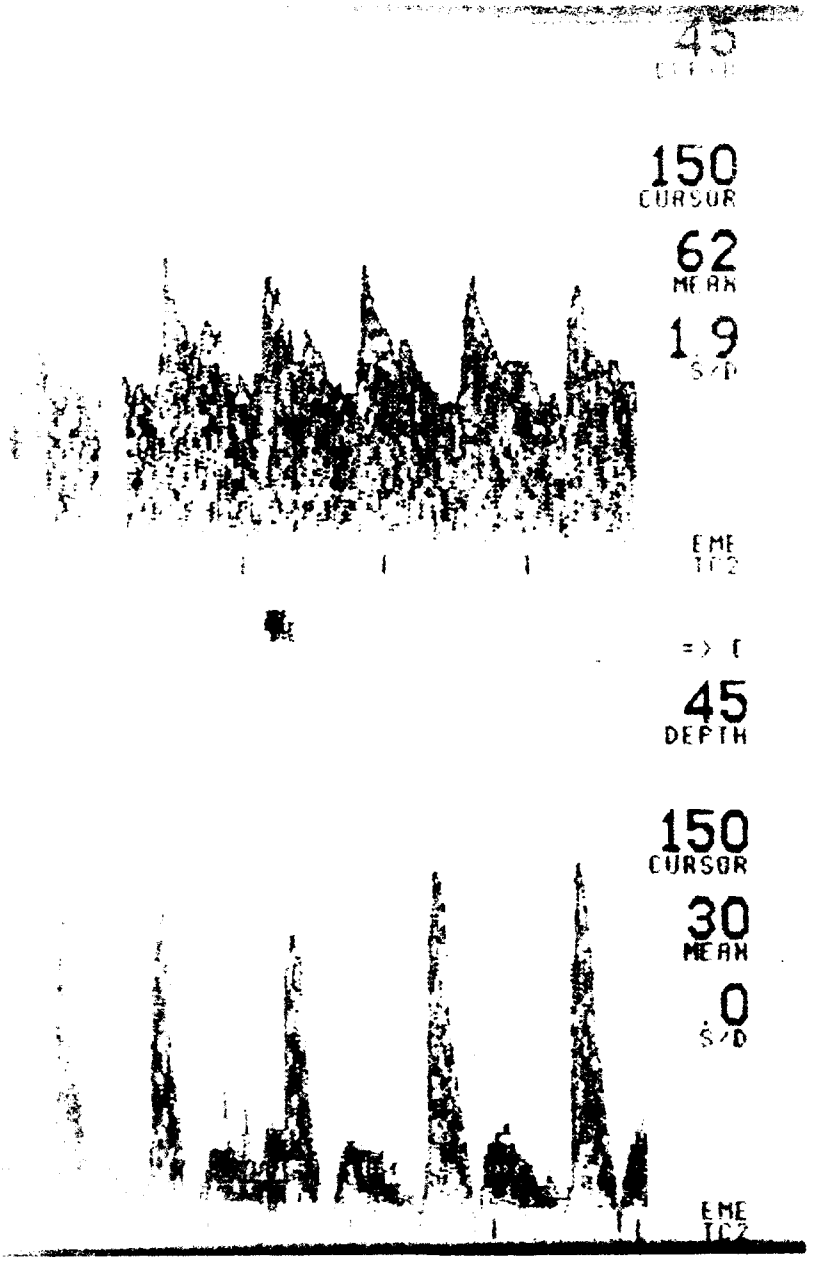

Figure 18. Examples of intolerant responses during lower body negative pressure as revealed by transcranial Doppler monitoring of middle cerebral artery flow. Nonbradycardiac intolerance is illustrated. Intolerance (bottom view) was marked by a fall in diastolic flow velocity between rest and the intolerant endpoint. Often this depression of diastolic velocity would persist long into recovery. Systolic velocity was often higher than that measured at rest. Intolerance was marked by extreme widening of the systolic-to-diastolic ratio, to ratios of nine or higher.

B. Intolerance to lower body negative pressure

Resting transcranial velocity profiles were indistinguishable in tolerant and intolerant subjects. However, intolerance was marked by a progressive and significant fall in both the diastolic (44.12 + 8.9 to 33.6 + 11.6 cm/s, $P < .05$) and mean (56.7 + 10.5 to 42.9 + 11.9 cm/s, $P < .05$) transcranial velocities, with subsequent significant widening of the systolic to diastolic ratio from rest-to-peak tolerated stress (2.03 + 0.2 to 2.32 + .38, $P < .01$). Often, but not always, this widening of the S to D ratio correlated with systemic hypotension and bradycardia.

		AVERAGE THROUGHPUT (learning curve)				SUM THROUGHPUTS (learning curve)			
PT		**1.0**	**2.0**	**3.0**	**4.0**	**1.0**	**2.0**	**3.0**	**4.0**
BAK		14.2	19.1	23.1	18.7	85.5	114.3	138.5	112.0
BUR		15.9	18.7	22.9	25.6	95.6	112.1	137.5	153.5
HAR		9.6	19.2	13.2	12.4	57.4	115.0	79.4	74.4
MCG		11.6	9.5	12.1	10.7	69.3	56.9	72.5	64.2
ODE		34.1	31.1	32.3	30.4	204.7	186.5	193.7	182.6
PIN		38.9	45.3	41.5	54.0	233.6	271.7	249.0	323.8
RUS		22.2	21.0	24.1	23.4	132.9	126.0	144.4	140.3
SEL		28.3	27.4	24.0	23.5	169.6	164.2	143.8	141.0
WEG		21.1	21.1	31.6	33.0	126.4	126.6	189.8	198.0
WES		24.7	24.9	33.5	31.3	148.2	149.5	201.1	187.6
	AVG	22.05	23.71	25.83	26.29	132.31	142.29	154.97	157.73
	STD	9.18	9.05	8.66	11.68	55.05	54.29	51.98	70.06

		STUDY #1 (AV THROUGHPUT)				STUDY #2 (AV THROUGHPUT)			
PT	**DRG**	**G1**	**GL1**	**A1**	**AL1**	**AL2**	**A2**	**GL2**	**G2**
BAK	P	19.9	20.4	25.5	26.3	15.6	17.2	18.0	18.9
BON	P	16.5	17.0	32.5	28.2	17.6	16.3	18.1	20.9
BUR	P	35.6	34.2	40.1	28.3	21.9	20.4	27.1	25.9
CLA	P	18.5	28.9	28.3	27.7	14.0	14.8	11.7	14.1
GAR	P	23.0	32.1	32.8	42.9	18.9	27.8	26.7	33.3
HAR	P	13.6	19.1	22.4	26.2	14.2	12.4	12.0	10.8
HEN	P	38.8	37.7	40.9	38.8	27.9	29.6	26.8	26.3
PIN	P	52.4	59.7	60.8	67.1	28.4	34.7	28.8	31.5
PNK	P	30.5	33.8	40.4	39.0	26.0	35.3	25.5	30.8
RUS	P	34.6	27.0	42.1	28.6	11.6	20.5	18.8	32.0
PLACEBO	**AVG**	22.0	24.7	25.2	23.3	19.6	22.9	21.3	24.4
PLACEBO	**STD**	11.6	11.7	10.4	12.1	5.8	7.9	6.1	7.5
BIR	B	18.4	20.6	31.7	31.0	4.6	19.2	20.3	22.8
BOU	B	15.6	21.4	21.0	18.8	11.7	12.2	13.7	13.2
GRI	B	24.4	19.8	23.8	21.9	10.8	15.8	16.4	14.8
MCG	B	10.1	11.9	15.0	13.9	11.6	17.6	11.5	27.8
ODE	B	42.2	48.0	55.9	37.2	27.0	31.9	37.5	36.6
POM	B	22.9	20.9	21.6	21.4	16.2	21.0	19.5	27.4
SEL	B	22.4	18.2	26.3	25.6	14.8	20.4	18.1	17.6
WAL	B	19.1	21.7	23.5	27.6	17.6	19.4	17.5	23.4
WEG	B	21.0	23.1	28.4	23.7	14.7	26.7	25.6	20.9
WES	B	27.0	49.5	38.9	38.7	24.5	32.6	29.7	80.8
BETA	**AVG**	22.3	21.2	22.6	20.0	15.3	21.7	21.0	23.5
BETA	**STD**	8.0	12.0	11.0	7.5	6.2	6.4	7.5	6.9

Table VI. Cognitive Responses. (Sorted By Treatment And Test Conditions.)

		STUDY #3 (AV THROUGHPUT)				STUDY #4 (AV THROUGHPUT)			
PT	**DRG**	**G3**	**GL3**	**A3**	**AL3**	**AL4**	**A4**	**GL4**	**G4**
BAK	B	16.0	17.4	13.9	18.0	14.1	15.1	17.2	20.9
BON	B	10.3	13.8	21.3	24.9	18.2	14.4	20.0	21.9
BUR	B	13.2	18.5	19.5	16.8	20.9	15.6	22.8	18.9
CLA	B	16.0	19.6	14.5	15.1	21.9	17.3	16.6	19.8
GAR	B	22.6	42.4	26.6	22.6	25.6	32.6	24.9	34.6
HAR	B	12.6	11.8	23.7	13.6	13.7	14.5	15.7	19.9
HEN	B	24.4	24.2	27.3	20.8	19.2	24.8	21.8	26.1
PIN	B	40.4	45.0	49.9	48.7	21.6	44.6	40.6	40.1
PNK	B	32.3	34.6	29.1	33.8	20.2	32.4	27.2	27.8
RUS	B	16.3	22.7	29.6	13.5	20.6	21.7	21.8	23.7
BETA	**AVG**	20.4	25.0	25.5	22.8	19.6	23.3	22.9	25.4
BETA	**STD**	9.1	11.1	9.7	10.4	3.4	9.7	6.9	6.7
BIR	P	25.0	27.3	30.6	22.0	18.9	20.9	25.4	20.4
BOU	P	11.9	12.9	14.6	17.5	12.2	18.5	14.2	14.7
GRI	P	15.2	15.1	25.5	18.9	14.1	18.2	16.7	27.4
MCG	P	19.2	18.8	18.7	11.2	9.8	18.5	9.2	20.8
ODE	P	31.7	33.6	34.6	32.2	32.5	31.2	28.7	29.6
POM	P	15.5	19.2	15.0	17.3	16.8	21.4	22.2	21.6
SEL	P	19.1	17.4	23.2	19.5	16.2	22.8	25.7	29.7
WAL	P	13.6	15.8	19.0	20.0	15.2	16.4	18.5	21.0
WEG	P	16.6	20.4	28.9	24.4	14.3	20.9	27.2	26.8
WES	P	27.5	25.5	29.8	29.5	28.4	31.0	20.1	26.7
PLACEBO	**AVG**	21.9	20.6	24.0	21.3	17.8	22.0	20.8	23.9
PLACEBO	**STD**	6.2	6.0	6.6	5.8	6.8	4.9	5.9	4.6

Table VI (Continued). Cognitive Responses. (Sorted By Treatment And Test Conditions.)

However, some responses were recorded with no bradycardia, but a widening in the S to D ratio (Figure 18).

Frequently, the intolerant endpoint was preceded 2 to 3 minutes by a detectable increase in the S to D ratio of the transcranial velocity profile. Frequently, the investigators were warned of impending intolerance by progressive widening of this ratio from resting values.

Cognitive Responses (Table VI)

A. The learning curve

All subjects manifest a distinct learning curve during administration of this abbreviated Walter Reed performance battery. Average throughput values (correct responses/minute) for subjects representing the upper, middle, and lower terciles of performance on the battery showed average throughput values of 22.05 + 9.2, 23.8 + 9.1, 25.8 + 8.7, 26.3 + 11.7 for repeated administrations spaced by 40 minutes, respectively. These data showed a gradual improvement of response from applications 1 to 2, and 2 to 3, then with a slower rate of response from 3 to 4. This slowing of the rate of improvement appeared to indicate either fatigue or a plateau in the learning curve.

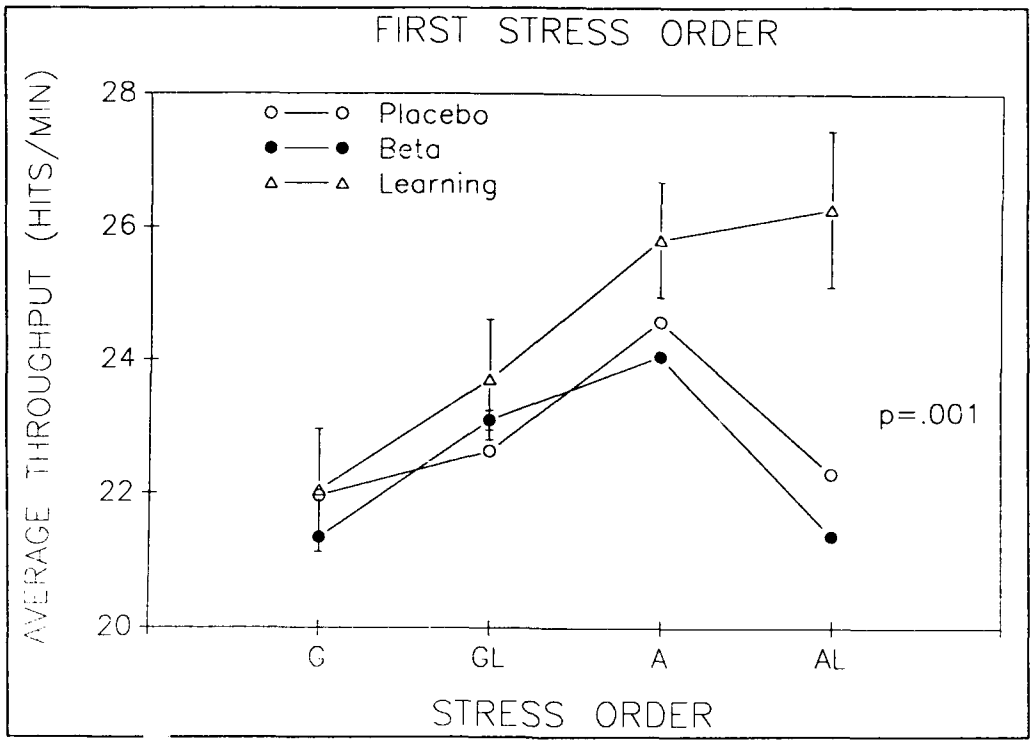

Figure 19. Cognitive response of placebo and beta-blocked subjects during ground unstressed (G), ground lower body negative pressure testing (GL), altitude unstressed (A) and altitude plus lower body negative pressure stress (AL) conditions. Only during AL stress was cognitive function impaired compared to the learning curve.

B. Stress order #1 (Figure 19)

The first order of stressors was applied on testing days 1 and 3. The order was unstressed cognitive testing, exercise, and then cognitive testing during lower body negative pressure, first at ground and then at altitude. Responses under these four conditions can be compared to the four sequential applications of the battery under unstressed conditions characterizing the learning curve. Average throughput responses for both beta-blocker and placebo treated subjects were no different than the learning curve for administrations 1 thru 3. Thus, at ground there was no detectable effect from lower body negative pressure, and at altitude there was no detectable effect without LBNP. However, when lower body negative pressure was applied at altitude, both placebo and beta-blocker subjects showed an equivalent departure from the learning curve (22.5 + 7.4 and 21.3 + 8.4 vs 26.3 + 11.7) with impaired cognitive performance significant at the $P < .001$ level.

C. Stress order #2 (Figure 20)

On test days 2 and 4, the subjects underwent lower-body negative pressure with cognitive testing, and then unstressed cognitive testing first at altitude and then at ground. The responses during this sequence were compared to the learning curve. The first application of the battery was in the most stressed condition, consisting of both altitude and lower body negative pressure. This combination of stressors showed a marked decrement in cognitive performance, compared to the learning curve ($P < .001$). However, this decrement was no different for beta-blocker or placebo-treated subjects (17.2 + 6.8 vs 18.5 + 7.4). In the second administration, unstressed at altitude, the cognitive performance of both placebo and beta-blocker subjects returned within the range of the learning curve.

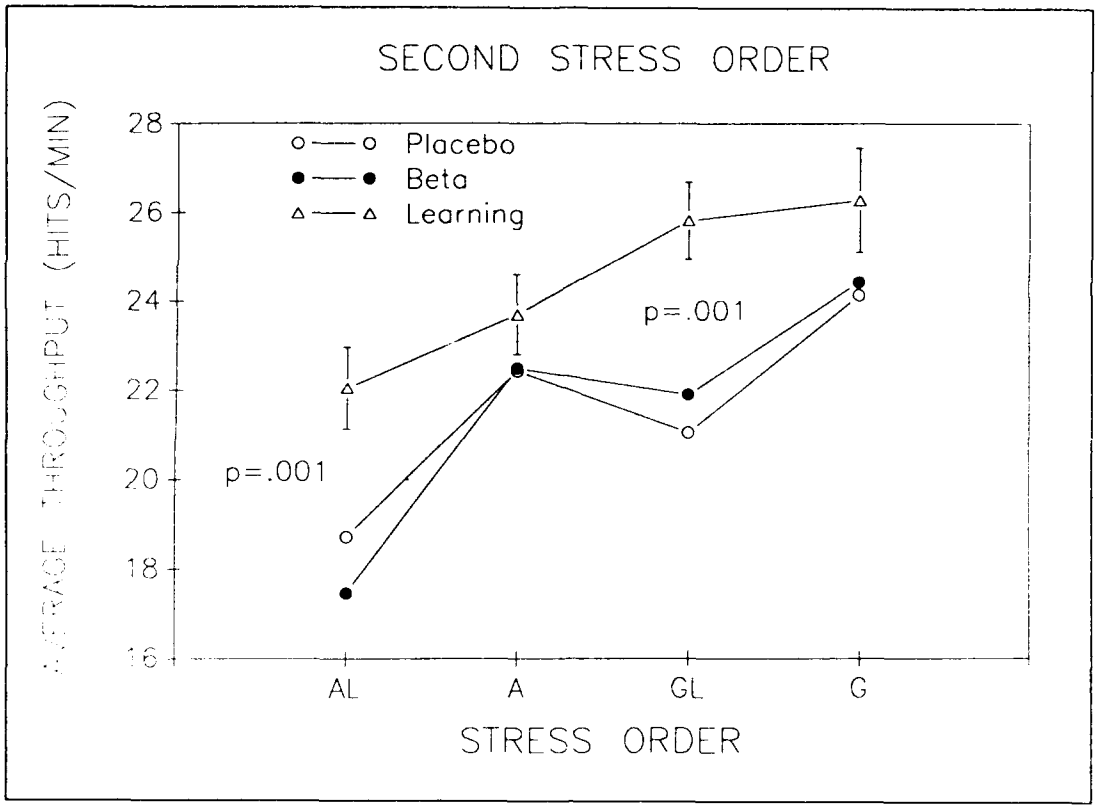

Figure 20. Cognitive performance, as expressed by average throughput, plotted as a function of the second stress order and compared to the learning curve. Lower body negative pressure stress both at altitude and ground onditions significantly impaired cognitive performance in the second stress order.

However, the third application, at ground during lower-body negative pressure, again showed a marked reduction in cognitive throughput for both beta-blocker and placebo-treated subjects (21.7 + 6.4 and 20.8 + 7.8 vs 25.8 + 8.7, P <.001). This effect may be ascribed to the stresses of lower-body negative pressure, or it may represent the cumulative fatigue experienced in the prior altitude testing. However, the fatigue hypothesis is thrown into doubt by the fourth administration of the test, at ground and without the stress of lower body negative pressure. Both placebo-treated subjects and beta-blocker subjects were within 1 standard deviation from the mean of learning curve during this condition.

Correlates of Intolerance

A. Pretest measurements. (Table VII)

Supine resting blood pressure was higher in placebo treated versus beta-blocker subjects for all 80 testing sessions (140/92.5 + 15.8/15.9 vs 130/83 + 15.9/9.9, P=ns). The orthostatic rise in pulse rate going from supine to standing positions was lower in beta-blocker subjects (64.5 + 7.5 to 67.8 + 8.4 vs 80 + 10.6 to 85 + 9.8, P < .001). However, sorting these data on the basis of tolerance or intolerance to subsequent lower body negative pressure, the pretest orthostatic blood pressure and pulse measurements of the 35 intolerant subjects were not predictive.

	SUPINE				STANDING			
MEANS	**BPS**	**BPD**	**BPM**	**HR**	**BPS**	**PD**	**BPM**	**HR**
N = 40 PLACEBO	140.	92.5	108.0	80.0	141.	95.5	110.	85.0
N = 40 BETA	130.	83.3	98.8	64.5	129.	88.7	102.	67.8
N = 55 TOL	138.	88.7	105.0	72.9	139.	93.8	108.	76.8
N = 35 INTOL	131.	86.6	101.0	71.3	130.	89.6	103.	75.7
STANDARD DEVIATIONS								
N = 40 PLACEBO	15.8	8.41	9.55	10.6	17.9	6.74	9.25	9.82
N = 40 BETA	15.9	9.95	11.2	7.46	17.2	11.1	11.5	8.38
N = 55 TOL	17.8	9.32	11.1	11.9	18.6	7.99	10.0	12.2
N = 35 INTOL	14.2	11.50	11.6	12.0	16.9	11.6	12.1	12.8

Table VII. Prestress Orthostatic Blood Pressure and Pulse. (Sorted By Treatment And Tolerance.)

B. Post-test measurements (Table VIII)

After the altitude chamber runs and ground level testing, the subjects collected 24-hour urine for the determination of the fractional excretion of sodium. Sodium excretion values were no different between placebo and beta-blocker subjects. In addition, fractional excretion of sodium failed to discriminate subjects that had been intolerant to lower body negative pressure from those who were tolerant (.73 + .18 vs .67 + .19). Twenty-four hour ambulatory blood pressure monitoring showed lower values for systolic blood pressure (122 + 10.6 vs 130 + 19.8, P=ns), diastolic blood pressure (77.2 + 8.9 vs 82 + 8, P=ns), and mean heart rate (64 + 7.3 vs 74 + 9.2, P < .001) in beta-blocker versus placebo-treated individuals. Sorting the data on the basis of tolerance or intolerance to lower body negative pressure, the tolerant subjects had insignificantly higher values for systolic blood pressure (126 + 19 vs 125 + 11), diastolic blood pressure (82 + 9 vs 78 + 8), and heart rate (70 + 10 vs 68 + 9) than those of intolerant subjects. In view of the lack of statistical significance, these mean 24-hour blood pressure and heart rate values cannot account for the 35 orthostatic intolerant runs. Hematocrit did not predict intolerance either (46.6 + 3.4 vs 47.7 + 3.9).

SUMMARY

In summary, the following answers to the key questions presented in the introduction were provided.

1. Beta-blockade in this double-blind randomized placebo controlled cross-over study caused a modest impairment in orthostatic tolerance. Five of the 80 lower-body negative pressure runs at ground level were marked by intolerance, and all of those responses were in beta-blocker subjects. Of the 80 altitude runs, 30 were terminated for intolerance, and 18 were attributable to beta-blockade. These findings had a Chi-square significance value of P < .05.

2. Altitude is a potent factor, potentiating orthostatic intolerance. Of the 35 intolerant runs, 30 of those were recorded at altitude. The effect of altitude was significant at P < .01 level.

3. In a modest exercise protocol, meant to be no more stressful than the exertional requirements of piloting an aircraft during adverse conditions, neither beta-blockade nor altitude appeared to limit performance. All subjects were capable of exercising to 100 watts, and maintaining that exercise level for 3 minutes, even at a simulated altitude of 12,500 feet.

4. Quantitative performance on the Walter Reed cognitive battery clearly demonstrated impaired performance during lower body negative pressure stress at altitude. The degree of impairment was significant compared with a learning curve response at the P < .001 level. The degree of impairment was similar for placebo-treated and beta-blocker subjects. The significant contributing factor to cognitive dysfunction during LBNP at altitude was sudden incapacitation. This phenomenon often resulted in cognitive collapse and inability to continue cognitive testing even though the orthostatic stress had been released. In no set of testing conditions could a cognitive impairment effect be demonstrated due to beta-blockade alone.

# PT	BAT	DRG	TOL	24 HR AMBULATORY MONITORING MEAN BPS	MEAN BPD	MEAN HR	SDEV BPS	SDEV BPD	SDEV HR	HCT	FRACTIONAL SODIUM
TOLERANT GROUP											
BON 1	P		Y	149	80	71	27	29	23	47	0.579
BON 2	P		Y	121	73	67	17	11	13	43	0.422
BON 3	B		Y	116	79	61	12	11	10	47	0.764
BON 4	B		Y	127	70	62	12	9	9	45	0.656
BOU 2	B		Y	118	83	68	18	16	14	49	0.758
BOU 4	P		Y	130	86	77	27	23	16	51	0.456
BUR 1	P		Y	139	100	75	11	11	14	45	0.712
BUR 2	P		Y	139	89	78	7	8	15	44	0.456
BUR 4	B		Y	114	91	63	9	7	10	44	0.627
CLA 1	P		Y	125	91	85	12	11	13	39	0.455
CLA 2	P		Y	147	96	77	12	12	12	40	1.169
CLA 4	B		Y	123	92	68	16	11	10	45	0.63
GAR 1	P		Y	142	78	75	22	15	15	47	1.162
GAR 2	P		Y	138	81	64	13	14	16	47	0.777
GAR 4	B		Y	127	78	57	17	11	11	49	0.63
GRI 1	B		Y	163	92	58	32	51	10	49	0.692
GRI 3	P		Y	150	74	54	19	15	10	51	0.615
GRI 4	P		Y	143	72	55	20	13	14	50	0.8
HAR 1	P		Y	125	83	97	32	28	33	41	0.774
HAR 4	B		Y	107	78	62	11	9	12	45	0.595
HEN 1	P		Y	133	80	97	24	22	21	49	0.383
HEN 2	P		Y	131	82	86	13	10	24	52	0.643
HEN 3	B		Y	125	66	76	9	9	12	43	0.603
McG 2	B		Y	108	76	62	14	12	11	43	0.496
McG 4	P		Y	116	77	78	11	9	13	43	0.359
ODE 1	B		Y	110	68	76	9	9	14	41	0.68
ODE 2	B		Y	109	67	65	14	11	13	43	0.882
ODE 3	P		Y	114	75	71	17	10	16	44	0.911
ODE 4	P		Y	123	86	87	15	10	18	43	0.865
PNK 1	P		Y	121	89	74	9	9	15	50	0.756
PNK 2	P		Y	138	87	63	15	12	13	52	0.712
PNK 3	B		Y	118	69	60	12	10	7	43	0.516
PNK 4	B		Y	116	73	62	16	12	8	45	0.661
PIN 1	P		Y	123	83	69	16	16	13	48	0.756
POM 3	P		Y	28	86	83	16	12	14	46	0.606
POM 4	P		Y	118	88	75	15	11	14	50	0.297
SEL 2	B		Y	114	76	55	13	11	12	45	0.888
SEL 3	P		Y	130	80	66	12	13	16	45	0.919
SEL 4	P		Y	135	84	70	18	14	17	46	1.056
WAL 1	B		Y	147	98	71	20	19	14	51	0.621
WAL 2	B		Y	126	97	68	11	20	8	50	0.41

Table VIII. Poststress Clinical Monitoring. (Sorted By Tolerance To LBNP.)

24 Hr AMBULATORY MONITORING

# PT	BAT	DRG	TOL	MEAN BPS	MEAN BPD	MEAN HR	SDEV BPS	SDEV BPD	SDEV HR	HCT	FRACT. SODIUM
WAL 3	P		Y	132	97	82	10	10	13	48	0.825
WAL 4	P		Y	158	89	72	22	15	29	50	0.736
WEG 3	P		Y	141	84	67	10	11	12	46	0.754
WES 1	B		Y	114	79	67	15	17	6	51	0.607
WES 2	B		Y	124	68	63	13	8	13	53	0.369
WES 3	P		Y	128	85	73	12	6	16	51	0.647
WES 4	P		Y	125	61	58	13	7	11	48	0.62
TOL=49	MEANS			126	81.58	70.20	15.41	13.54	14.02	46.60	0.673062
	SD			19.36	9.167	10.00	5.670	7.334	5.018	3.468	0.192081

INTOLERANT GROUP

# PT	BAT	DRG	TOL	T	MEAN BPS	MEAN BPD	MEAN HR	SDEV BPS	SDEV BPD	SDEV HR	HCT	FRACT. SODIUM
BAK 1	P		N	13:21	137	86	75	16	13	20	51	0.699
BAK 2	P		N	12:20	152	89	70	18	13	18	50	0.833
BAK 3	B		N	19:15	130	83	72	13	9	12	50	0.779
BAK 4	B		N	14:30	126	84	66	17	14	19	51	0.834
BIR 1	B		N	13:45	125	83	77	21	20	11	51	0.908
BIR 2	B		N	3:30	117	81	70	11	9	11	52	0.896
BIR 3	P		N	13:30	136	82	86	15	13	19	53	0.65
BIR 4	P		N	14:00	131	96	78	18	13	15	53	0.722
BOU 1	B		N	19:20	125	78	73	16	12	10	51	0.443
BOU 3	P		N	19:00	136	84	76	18	10	25	52	0.557
BUR 3	B		N	12:20	140	84	63	11	11	10	43	0.991
CLA 3	B		N	19:00	123	88	66	11	11	5	37	0.695
GAR 3	B		N	18:40	125	71	54	13	10	11	46	0.322
HAR 2	P		N	13:30	109	77	76	14	12	17	49	0.83
HAR 3	B		N	14:30	105	78	60	11	9	13	47	0.777
HEN 4	B		N	18:30	121	68	66	9	8	12	46	0.641
McG 1	B		N	13:00	123	82	82	27	25	13	44	0.526
McG 3	P		N	10:00	115	84	85	8	7	15	39	0.871
PIN 2	P		N	18:30	132	79	64	12	13	15	51	1.21
PIN 3	B		N	19:30	121	71	50	12	13	12	45	0.95
PIN 4	B		N	18:20	118	69	50	17	8	12	46	0.789
POM 1	B		N	18:30	121	69	61	15	15	10	45	0.574
POM 2	B		N	19:30	126	80	63	13	11	14	43	0.888
RUS 1	P		N	17:00	130	66	68	24	10	12	48	0.575
RUS 2	P		N	15:30	119	70	73	13	10	20	49	0.695
RUS 3	B		N	18:30	116	62	55	7	7	11	46	0.709
RUS 4	B		N	13:20	118	67	58	7	8	27	46	0.692
SEL 1	B		N	19:40	115	71	62	8	7	9	46	0.846
WEG 1	B		N	15:00	125	82	72	12	11	26	53	0.593
WEG 2	B		N	17:30	122	74	62	11	9	10	47	0.502
WEG 4	P		N	16:30	147	84	69	10	11	15	50	0.65
INTOL =31	MEANS				125.3	78.12	67.80	13.80	11.35	14.48	47.74	0.730548
	SD				10.09	7.852	9.215	4.631	3.676	5.098	3.918	0.176848

Table VIII (Continued). Poststress Clinical Monitoring. (Sorted By Tolerance To LBNP.)

5. It does appear feasible to simulate the stresses of aviation, namely vertical acceleration and altitude, in a controlled ground-level testing environment utilizing hypobaric hypoxia and seated lower body negative pressure stress. Utilizing modest levels of lower body negative pressure meant to simulate 2G of sustained vertical acceleration at a simulated altitude of 12,500 feet, 30% (placebo cases) to 45% (betablocker cases) of trials can be expected to cause sudden incapacitation and intolerance.

6. Utilizing current technology, it is very possible to perform noninvasive hemodynamic monitoring in subjects undergoing altitude and orthostatic stress. Noninvasive monitoring of mean arterial pressure, heart rate, and stroke volume is necessary for quantitative analysis of hemodynamic responses to these stressors. These parameters demonstrate progressive decrements in systemic vascular resistance in intolerant subjects, implicating a defective peripheral autonomic nervous system response. In intolerant subjects, the peripheral autonomic nervous system appears to be incapable of increasing vascular tone in response to increasing orthostasis. Intolerance is not due to a cardiodepressor reflex, as commonly believed. Moreover, monitoring of systemic vascular resistance, blood pressure, and transcranial middle cerebral artery flow velocities allows prediction of impending cognitive and hemodynamic collapse. Collapse is marked by falling middle cerebral diastolic flow velocity, a widening of the systolic-to-diastolic ratio, and systemic hypotension. Simultaneous cognitive testing with a quantitative performance battery mirrors orthostatic intolerance by a profound reduction in correct responses per minute.

7. No common clinical parameter, such as hematocrit, state of hydration, average 24-hour blood pressure, or supine-to-standing blood pressure or pulse rate predicts subsequent intolerance. The most predictive index of orthostatic tolerance is prior proven ability to withstand orthostatic stress.[44] [45]In the current study, 5 subjects accounted for over 50% of the intolerant responses. Thus, within the hypertensive population at large, there exists a subpopulation at high risk for orthostatic intolerance during beta-blockade and altitude exposure. It appears that only formal stress testing will uncover these orthostatis-prone individuals.

Limitations

The duration and rate of increase of the orthostatic stress imposed by LBNP were not representative of the stresses encountered in the general aviation environment. Although +2 Gz is commonly experienced in the aviation environment, usually this level of acceleration is reached much more rapidly and is of much shorter duration. It is possible that our lower body negative pressure protocol caused more extensive pooling in the lower extremities over the 20-minute stress period, resulting in more pronounced orthostasis than might be experienced during nominal civilian flight. Moreover, lower body negative pressure testing only approximates the full orthostatic stress of vertical acceleration. The augmented stress is simulated by the production of vascular pooling in response to negative pressures applied to the lower extremities. This regional effect may be different from a distributed effect of augmented acceleration forces acting on every unit of blood within the vascular tree. Nonetheless, anticipated falls in mean arterial pressure, rises in heart rates, and falls in stroke volume were produced that mimic the +2Gz responses seen in human centrifuge runs.[24]

A second limitation of this study was the lack of a beat-to-beat methodology for monitoring blood pressure. It was possible to monitor all other physiologic parameters such as heart rate, stroke volume, and Doppler ejection indices in a continuous and uniform fashion so that clear trends were apparent long before hemodynamic collapse occurred. The addition of beat-to-beat assessment of noninvasive blood pressure would be a welcome addition, as it would afford early warning of falling blood pressure.

The third limitation of the study was the apparent insensitivity of the cognitive battery to the potentially potent effects of lower body negative pressure and altitude. Significant reductions in cognitive performance were found only during periods of orthostatic intolerance induced by lower body negative pressure at altitude and ground. These findings may warrant a closer look at the scoring scheme or test design of such batteries for the assessment of performance in the aviation environment.

The final limitation of this study was the essential cost and complexity of the testing protocol. Duplication of this protocol would require access to a hypobaric chamber capable of at least 12,500 feet altitude, a custom lower body negative pressure stress testing plethysmograph, and approximately $40,000 worth of noninvasive hemodynamic monitoring equipment, as well as the cost of personnel to staff the hypobaric chamber and perform the stress protocol. Safety reasons mandate that the hemodynamic monitoring must be maintained.

Clinical Implications

These data implicate the synergistic deleterious effects of beta-blockade and altitude in the potentiation of intolerance to orthostatic stress. These findings may have most revelance to the personnel of unpressurized

aircraft who are treated for hypertension with beta-blocking drugs. Further study of drugs that deplete the vascular space, block the renin-angiotensin system, inhibit the central vasomotor center, or act as noncardioselective beta-blockers may be warranted.

A second finding of clinical revelance is the existence of a high-risk subgroup with provokable orthostatic intolerance within the general hypertensive population. These individuals have no prior history of syncope or orthostatic intolerance. Such individuals have reproducible intolerance to lower body negative pressure testing. Should other pharmacologic agents prove to be less provocative of orthostatic intolerance than beta-blockers, orthostatic testing of the hypertensive aviator may be warranted to tailor antihypertensive medications according to orthostatic tolerance.

The final implication of the study is that the parameter most likely to enhance orthostatic tolerance is uncontrolled systemic hypertension. Although not statistically significant, we observed that the most tolerant subjects had the highest blood pressures at the initiation of lower body negative pressure testing. This finding may warrant further investigation. If corroborated, the implication would be that some trade-off between antihypertensive control and orthostatic tolerance may be needed.

Future Work in This Area

In an attempt to improve the economics and proliferation potential of such testing, a study aimed at the evaluation of a hypoxic gas mixture and tilt table orthostatic testing might be considered. Such a streamlined testing protocol would obviate the need for a hypobaric chamber as well as a lower body negative pressure device. It may be possible to achieve similar physiologic stress by breathing a mixture of gases approximating the atmosphere at 12,500 feet, and performing orthostatic stress on a tilt table rather than a lower body negative pressure device. It would be possible to maintain noninvasive monitoring of hemodynamic and cerebral blood flow parameters in such a system and avoid the cost of a hypobaric chamber and lower body negative pressure testing equipment.

Regarding hemodynamic monitoring, the essential elements must be heart rate, mean arterial pressure, and stroke volume. A beat-to-beat method for the assessment for mean arterial pressure would enhance the hemodynamic monitoring of orthostatic stress testing. From these prime independent variables, hemodynamic characterization of cardiac performance and performance of the peripheral autonomic nervous system can be determined. Accessory and useful monitoring includes transcranial middle cerebral blood flow, and some estimate of pooling in the lower extremities in response to lower body negative pressure stress testing. We did not find Doppler assessment of left ventricular ejection an easy procedure to perform, and it offered no further information beyond the assessment of cardiac stroke volume already available from bioimpedance. More work appears justified for the development of cognitive batteries that are more sensitive to minor cognitive impairments induced by aviation specific stressors.

Of basic importance is a more general physiologic understanding of the phenomenon of orthostatic intolerance, and the development of pharmacologic means of ameliorating or abating such a response.[46] Such research would aim at selecting antihypertensive agents that do not inhibit orthostatic reflexes, possibly in combination with other agents that enhance the vasoconstrictive response of the peripheral autonomic nervous system in response to orthostatic stress.

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*U.S.GPO:1992-661-063/40046